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CONTENTS

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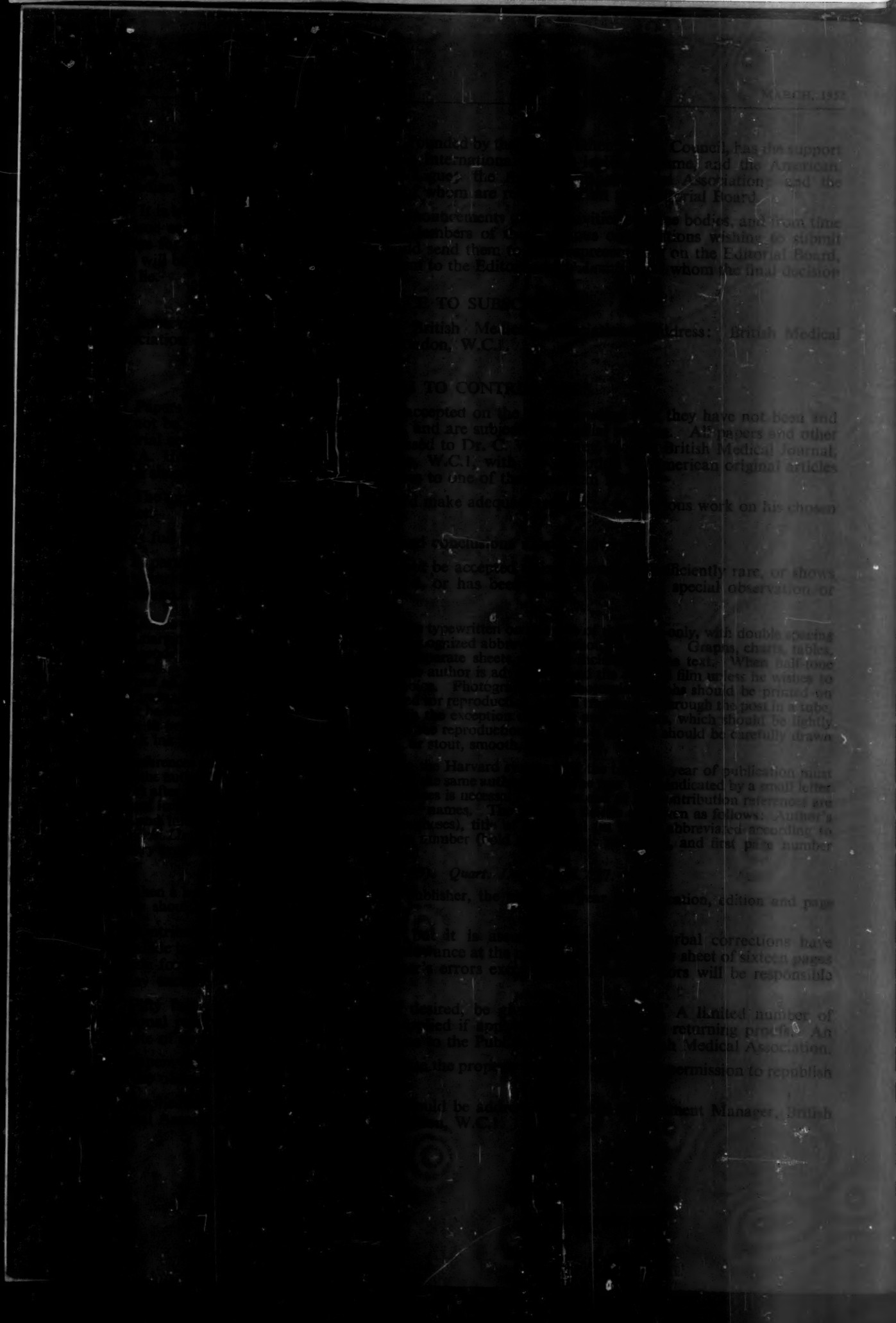

EDITORIAL

The Editorial Committee regret to have to report that the cost of publication of the *Annals* has risen to a serious degree; this is mainly due to the cost of paper which has twice doubled itself since January, 1951, while the cost of printing has also risen, and the size of the *Annals* has become substantially greater in the last few numbers.

An increase in the annual subscription has already been announced, and the possibility of effecting economies has also had serious consideration. While endeavouring to continue using the same quality paper for the original scientific articles and illustrations, it will be necessary to use a less expensive paper for the remainder, and to revert to the double-column arrangement for that part of the Journal dealing with the various anti-rheumatic societies and their activities. It is hoped that contributors will endeavour to be brief and to the point, and to remember that while illustrations are helpful, and, indeed, often indispensable, they should not be too numerous. The editors are always loth to cut down papers, but this may prove inevitable if these suggestions are not borne in mind.

The Committee gratefully acknowledge the encouragement and support they have received at all times from the Journal Committee of the *British Medical Journal*; they hope the proposals referred to above will lessen the financial burden while maintaining the standard of the *Annals* and its increasing circulation, which is already world-wide.

PERI-ARTHRITIS OF THE SHOULDER
STUDIES OF VEGETATIVE FUNCTION

BY

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(RECEIVED FOR PUBLICATION AUGUST 13, 1951)

Definition.—A diagnosis of peri-arthritis of the shoulder is made when a patient exhibits pain in the region of the shoulder and limited mobility of the joint, apparently of spontaneous onset or following slight injury. The *x*-ray appearances may show either nothing abnormal or calcific deposits in the capsule or peri-articular tissue.

This syndrome is not a disease *sui generis*, since the underlying pathological changes may no doubt affect either the joint capsule or the peri-articular tissue. Peri-arthritis of the shoulder, therefore, is a collective term for a number of different lesions of the shoulder, the only common features being pain and limitation of movement in the shoulder joint.

A common term may be used for the time being because the clinical features, regardless of the site of the morbid changes, which can hardly be determined without biopsy, are more or less uniform.

Previous Suggestions regarding the Causes of Peri-Arthritis of the Shoulder

Since Duplay (1872) described the syndrome as humeroscapular peri-arthritis, a number of papers have dealt with this lesion. Nevertheless, the actual cause or causes of the disease are obscure, as it is not yet definitely known *why* the morbid changes arise.

The methods used to elucidate these matters comprise (*a*) direct studies of the shoulder joint and peri-articular tissue at operation, by microscopical examination of biopsy specimens, and (*b*) clinical studies. In the latter connection it is most interesting to report the papers dealing with the common occurrence of peri-arthritis of the shoulder as a complication of certain other diseases with a constancy which makes it reasonable to presume a pathogenetic relationship.

(*a*) *Biopsy Studies.*—Neviaser (1945), studying biopsy specimens, found inflammatory changes in the subacromial bursa in seven out of ten cases, tenosynovitis in the long head of the biceps in ten cases, and the capsule adherent to the humeral head in all cases. Microscopical examination of the capsule failed to reveal any definite morbid changes in the synovial cells, but practically all cases exhibited chronic inflammation in the sub-synovial layers, characterized by fibrotic and degenerative processes in the connective tissue and in a few cases by calcification. Culture of the bacteria was negative. Owing to the constant capsular changes, Neviaser interpreted the lesion not as peri-arthritis, but as a thickening and contraction of the capsule which became adherent to the head of the humerus; he therefore suggested the term adhesive capsulitis.

Lippmann (1947), on the contrary, found tenosynovitis of the sheath of the long head of the biceps among twelve operated cases. He did not encounter changes in the sub-acromial bursa or in the peri-articular tissue. Microscopical examination showed inflammatory changes—hyperaemia, oedema, and hyperplasia of the connective tissue with leucocytic and lymphocytic infiltration. In Lippmann's opinion the pain is due to the inflamed tendon sliding freely in the joint proper, and he thinks that fusion of the synovial sheath and the tendon will result in a cure.

Simmonds (1949), working on biopsy specimens derived from operation in four cases, found the initial lesion to be a degenerative process in the supraspinatus tendon and inflammation of the capsule to be a later phenomenon. The cause of this degeneration is unknown, but he found necrotic areas in the tendon surrounded by an inflammatory process.

Though opinions are divided, it seems justifiable to derive from these studies the following conclusion:

The morbid changes in peri-arthritis of the shoulder may affect the joint capsule, or the peri-articular tissue, especially the sub-acromial bursa, the sheath of the long head of the biceps, and the supraspinatus tendon. The changes are nonspecific, suggesting chronic inflammation, and fibrotic and degenerative processes predominate, sometimes with calcification of the degenerated tissue.

Degenerated or necrotic tissue is known to be prone to calcify, and therefore we may assume that there is little fundamental difference between peri-arthritis of the shoulder with and without calcification. This view is held by most workers (Edström, 1936; Kahlmeter, 1936; Dickson and Crosby, 1932), and is supported by the fact that the symptoms often seem to bear little relation to calcifications, which may persist practically unchanged, although the symptoms have subsided. Other workers (Sandström, 1929, 1939; Thyge Madsen, 1948) incline to the view of a nosological entity though without advancing any definite reason.

(*b*) *Clinical Examination.*—This also fails to give a definite explanation, but some of the studies indicate that vegetative disturbances may be at any rate a predisposing factor and that they are in some cases without a doubt the chief cause of the morbid changes in peri-arthritis of the shoulder. In this connection a syndrome, now usually called the shoulder-hand syndrome, which was described by Kahlmeter (1936), is interesting: it comprised brachial neuralgia, peri-arthritis of the shoulder, vasomotor disturbances in the hand, and a state of fear. Kahlmeter advanced the hypothesis that the cause might be found in a local disturbance of the cervical sympathetic trunk, or of more central vegetative centres, or even possibly in neuritis of the sympathetic nerves. This hypothesis is supported partly by anatomical findings, partly by the effect of sympathectomy. The vasomotor disturbances appear in the form of trophic disturbances manifesting themselves as subcutaneous infiltration of the fingers and hand, the normal creases of the skin being smoothed out. A characteristic sign is also cyanosis interspersed with white patches affecting the hand and fingers, when the arm is hanging down. Often, hypaesthesia and hypalgesia may be found in small areas, and an almost invariable sign is marked limitation of motion in the finger joints and perhaps also in the wrist. Characteristically the elbow joint is hardly ever involved. The mobility in the shoulder joint is almost always very slight, but trophic disturbances like those observed in the hand and fingers are never encountered in the region of the shoulder. The disease is very prolonged and fairly incapacitating. As a rule, blocking of the stellate ganglion is tried, often successfully according to Steinbrocker and others (1948), and with improvement in 60 per cent. according to Jespersen (1949). Jespersen affirms, however, that the effect is equally good, whether or not the blocking results in Horner's syndrome, a finding which does not indicate that surgical intervention is wholly satisfactory.

(*c*) *Concurrent Disorders.*—Peri-arthritis of the shoulder as a complication of *angina pectoris* seems to have been first reported by Howard (1930), and in Scandinavia has

been dealt with mainly by Ask-Upmark (1944). These cases are often accompanied by trophic disturbances in the homolateral hand and fingers, i.e. it is often a shoulder-hand syndrome. Even in the absence of finger involvement, Steinbrocker interprets peri-arthritis of the shoulder in a patient with *angina pectoris* as an abortive shoulder-hand syndrome, claiming that it is a case of reflex dystrophy confined to the shoulder. The frequent coincidence of the two diseases might indicate that vegetative disturbances may predispose to peri-arthritis of the shoulder, since attacks of *angina pectoris* are elicited by vegetative impulses (vascular spasms). It is worth noting that the pains often radiate into the arms, particularly the left, and that patients with *angina pectoris* often suffer from sensations of fear during an attack.

The idea of a vegetative genesis is also supported by the fact that peri-arthritis of the shoulder is common in the presence of *Graves's disease*. Among 298 patients with hyperthyroidism, Duncan (1932) found 29 per cent. with articular symptoms. Iversen, Sindbjerg-Hansen, and Snorrason (1946) found peri-arthritis of the shoulder to be about 7 or 8 times more common among patients with Graves's disease than among normal persons. Snorrason and Duncan have suggested that hyperthyroidism might also be caused by disturbances in the vegetative central nervous system.

Cases of *epilepsy* treated with phenobarbitone sometimes develop peri-arthritis of the shoulder; this phenomenon, first described by Maillard and Thomazi, was later confirmed in Denmark by Lund (1943), who stated that besides peri-arthritis, such epileptics are also apt to develop Dupuytren's contracture, hilodermia, plastic induration of the penis, and fibroma of the soles of the feet. Since all these abnormalities are due to an increased tendency to form connective tissue, Lund is of the opinion that the pathological cause of peri-arthritis is a fibrotic process and calls all four conditions fibroblastic lesions. Fibrotic processes are almost invariably found in biopsy examination.

Peri-arthritis of the shoulder is also a common finding in cases of *psychosis* treated with phenobarbitone (Bandorf-Kullman, 1939), but it is a common complication in psychiatric cases, even without phenobarbitone medication, and it is not yet agreed whether the trophic disturbances are elicited by phenobarbitone, by the mental disorder, or by a combination of the two. Lund thinks it may be assumed that central vegetative disturbances play some part in its development.

Patients with *cerebral haemorrhage* occasionally develop a shoulder-hand syndrome which must presumably be interpreted as a result of damage to the central vegetative system. In five out of 42 patients with shoulder-hand syndrome examined by Steinbrocker and others (1948), the condition had developed after cerebral haemorrhage.

Among other complications, the patients sometimes also suffer from mild *anaemia*. In a series of 42 patients examined by Steffensen (1945), nine were anaemic, and four suffered from a co-existent *diabetes mellitus*; this series was selective, however, in that it comprised only hospitalized patients.

Pulmonary disorders have also been mentioned as frequently concurrent with peri-arthritis of the shoulder, and prolonged *rest in bed* is also said to be a predisposing factor. These latter phenomena, however, have not been submitted to further study.

Present Investigations

The present study was undertaken to find out whether tests of vegetative function (measurement of skin temperature) might be able to demonstrate vegetative disturbances in peri-arthritis of the shoulder, even in cases where no trophic disturbances were demonstrable. Since manifest vegetative disturbances occur in the presence of peri-arthritis of the shoulder (shoulder-hand syndrome), it is reasonable to try to find out whether abnormal vegetative impulses are demonstrable in the fingers even in the absence of visible vegetative disturbances. Such

studies are also thought to be justified by previous workers' findings regarding the co-existence of peri-arthritis of the shoulder with angina pectoris, Graves's disease, epilepsy, and cerebral haemorrhage.

Methods of Measuring Skin Temperature.—Measurement of the skin temperature as a means of studying the vasomotor reactions has been undertaken in various ways:

In Denmark Ipsen described a procedure which is usually called the cold test:

> For 10 minutes symmetrical parts of the extremities are immersed in water at 15° C. to produce arteriospasms. After the extremities have been removed from the water, the spasms will be relieved and the temperature will rise. By comparing the symmetrical sites, it is possible to demonstrate unilateral disturbances. This method, however, is rather inaccurate, since, amongst other reasons, the water remains on the limbs in small drops which evaporate and thereby cool the site after it has been removed from the water. This evaporation may easily vary on the two sides.

Gibbon and Landis recommended the following procedure:

> The patient is left in a cool room with the limbs to be examined exposed, so that the skin temperature falls evenly to approximately the room temperature. If the arms are to be studied, the lower limbs are then placed in a foot bath of 44° C. This results in an increase in the skin temperature of the arms after a certain latent period. In normal persons the increase takes place practically at the same time and to the same level on both sides (according to Gibbon and Landis to at least 31·5° in 30 min.).

After using this method in a few cases I abandoned it, because the decrease of temperature was far too slow, and was not marked enough, possibly because the room was not cold enough. Another disadvantage is that air currents may act upon the temperature at the sites to be examined and so cause inaccuracy.

I therefore adopted the method advocated by Christiansen, Fog, and Vanggaard (1939), which was later used for physiological studies by Vanggaard (1941), and formed the basis of the investigations of Haldbo (1942) into post-traumatic reflex dystrophy. The method is as follows:

> The arms are placed in a cold box where they remain throughout the experiment. When the skin temperature has decreased sufficiently (12-16° C.), vascular dilatation is induced by placing the feet into hot water (42-44° C.), which makes the skin temperature rise abruptly to a maximum after a certain latent period. The footbath is removed, and another gradual decrease in temperature occurs.

The cold box offers the advantages that air currents are practically excluded, evaporation from the skin is slight, and the same exogenous action is obtained on both sides; thus changes in skin temperature depend solely on variations in the blood flow through the skin. If the blood vessels are normal, the skin temperature must depend on the vegetative innervation. Comparison of the two sides, therefore, will demonstrate unilateral vegetative disturbances.

Haldbo used two boxes, the sides of which were filled with a mixture of ice and water, I used only one box in an endeavour to expose the arms to the same exogenous action.

The walls of the box consist of two layers of plywood separated by an insulating layer of glass wool. A quarter of an hour before the experiment is started, a zinc tray with ice is placed in the ceiling of the box; this tray is covered with a plate of zinc and provided

with a tightly-fitting lid of the same material as the floor and walls. The arms are inserted through two holes at one end of the box, and the holes are provided with felt cuffs which are tied—without pressure—round the patient's arms, so that the insulation remains effective. So that the measurements may be made under visual control, the other end of the box is fitted with double glass panes provided with two small holes, spaced about one shoulder-breadth apart, for insertion of the measuring instrument. These holes, which are plugged with cotton wool when not in use, are placed about 15 cm. above the fingers, so that air currents during the measurement may be presumed to be negligible. I used a thermo-element mounted on a handle and connected with a potentiometer showing the temperature directly. All the measurements were made in symmetrical sites on the right and left, on the dorsal aspect of the middle finger in the most distal extensor crease.

Because of technical and other difficulties no measurements were made on the shoulders. It is impossible to exert the same pressure at each measurement with thermo-elements which are not fixed; in the region of the shoulder the ample subcutaneous tissue exerts an effect, but this is of negligible importance in the fingers. It is impracticable to cool the shoulders in a cold box. The local inflammatory changes and consequent hyperaemia may be expected to give rise to vegetative disturbances as a purely secondary phenomenon, so that any findings on the shoulders are of only minor interest.

Material.—Tests of vegetative function were carried out on a total of thirty patients. The patients were selected, since it was not considered justifiable to let persons over a certain age sit with their arms in the cold during the 3 or 4 hours of the experiment. In addition, I preferred females to males, because in my experience females have decidedly more patience for such prolonged examinations. The age and sex of the thirty patients are shown in the following Table.

AGE AND SEX DISTRIBUTION OF PATIENTS

Sex		Age Group			
♀	♂	30-40	40-50	50-60	60-70
26	4	1	4	17	8

Of the thirty patients, one had a unilateral and two a bilateral shoulder-hand syndrome, but the remaining 27 did not exhibit trophic disturbances. At the time of the examination the two patients with bilateral shoulder-hand syndrome were in-patients in the neurological department, and all the rest were attending the department of physical therapy as out-patients.

Procedure.—It is important for the arms to have been exposed to a uniform exogenous action for some time before the experiment begins. This is of particular importance in the case of ambulant patients. Like Haldbo, therefore, I had to let the patients sit with the arms uncovered in the experimental room before the experiment was started.

During the experiment the skin temperature was measured at 5-min. intervals while it was decreasing, and at 2½-min. intervals while it was increasing in response to indirect heating.

The results of these studies have been plotted as curves (Figs 1-10), the abscissa showing the time in minutes and the ordinate the temperature in °C. The thick line parallel to the abscissa gives the duration of the footbath.

Results

A. Cases without Trophic Disturbances (27)

In 21 out of these 27 patients the skin temperature fell almost equally, and the increase in temperature occurred almost simultaneously, reaching the same level on both sides at the same time. The latent period from the time when the feet were immersed in water until the temperature began to increase varied widely—from 15 to 90 min. According to Vanggaard (1941), however, this latent period is subject to physiological variations, so that it does not allow of any conclusions regarding abnormal conditions. An example of one of these 21 curves is given in Fig. 1.

Among the 21 patients with little or no difference between the two sides, are two whose curves deserve consideration (Figs 2 and 3). These showed agreement

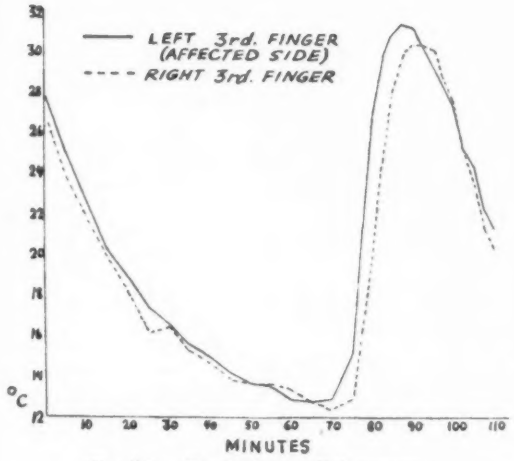


FIG. 1.—Typical parallel curves.

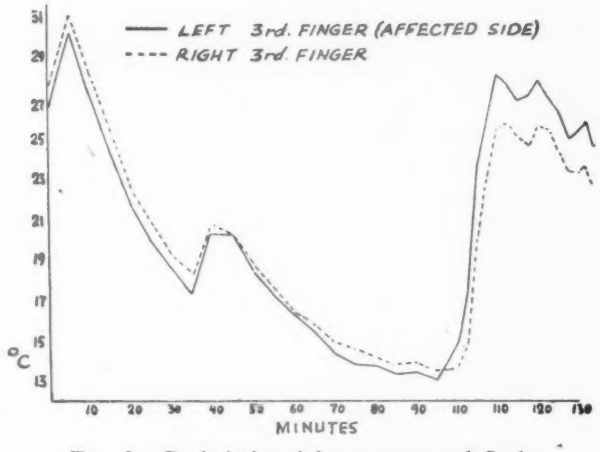


FIG. 2.—Peak induced by menopausal flush.

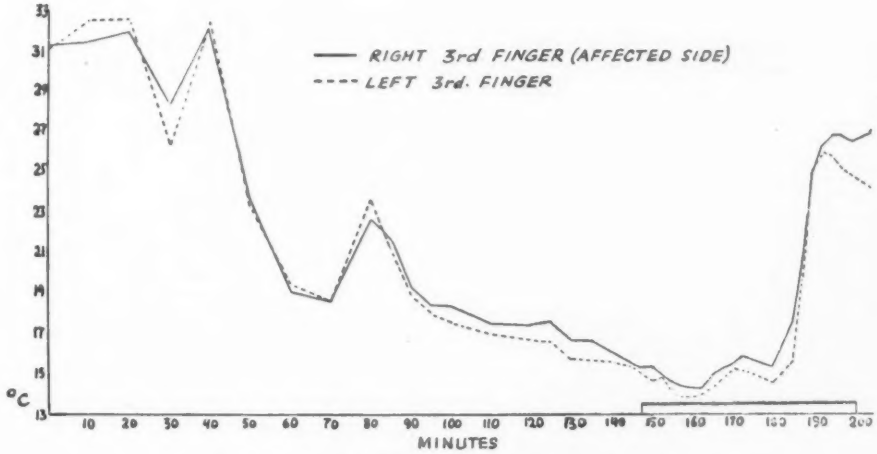
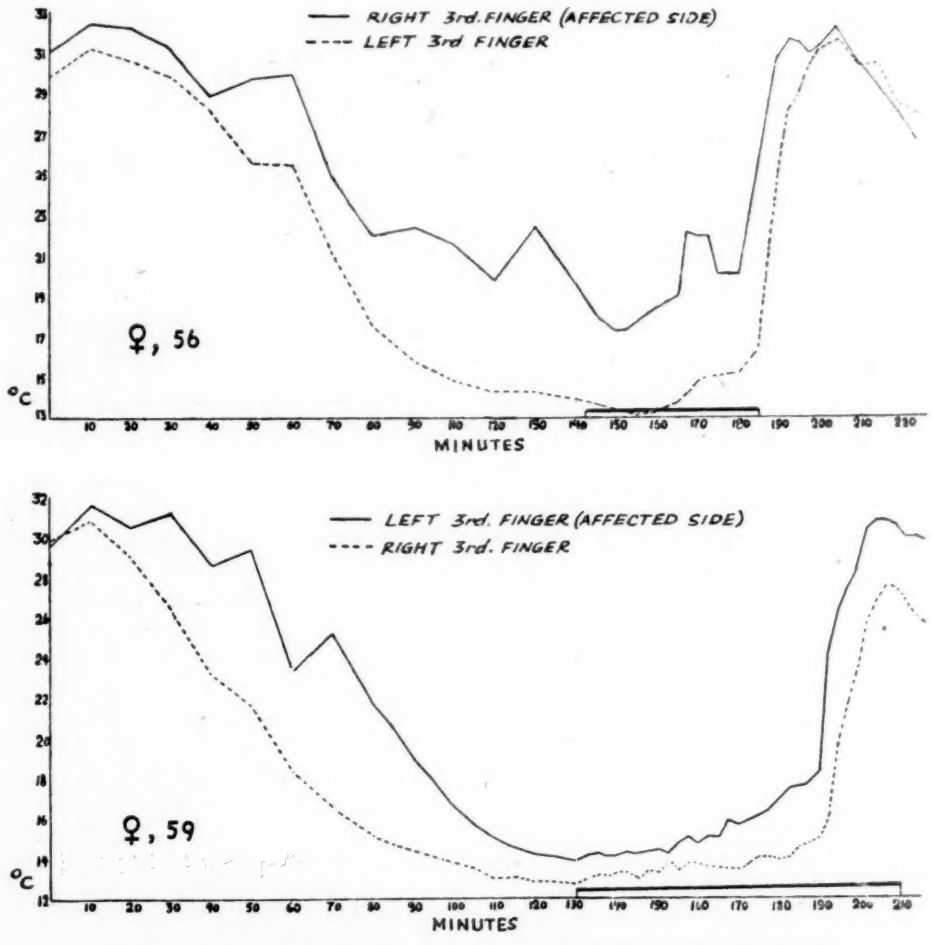


FIG. 3.—Peak induced by menopausal flush.

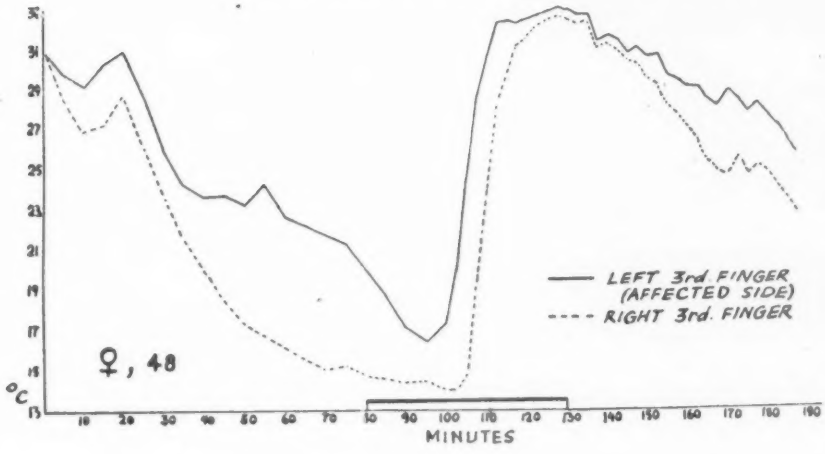
between the skin temperature on both sides, but after the temperature had fallen to about 20° C., there was a sudden " peak " representing an increase of about 5° C. In both cases about 30 min. elapsed before the temperature fell to the level at which the increase set in. It turned out that both patients had had menopausal hot flushes at the time when the temperature rose. These flushes resulted in marked vasodilatation on the fingers which lasted for half an hour. No further mention will be made of vegetative disturbances during the menopause.

The curves representing the other six patients, who showed more marked differences between the two sides, are given in Figs 4 to 9: of this group five (Figs 4 to 8) were much alike; the skin temperature on the affected side fell more slowly and not so far as on the healthy side. During the decrease, the difference amounted to 8 or 9° C., and in no case was the maximum difference less than 7° C.

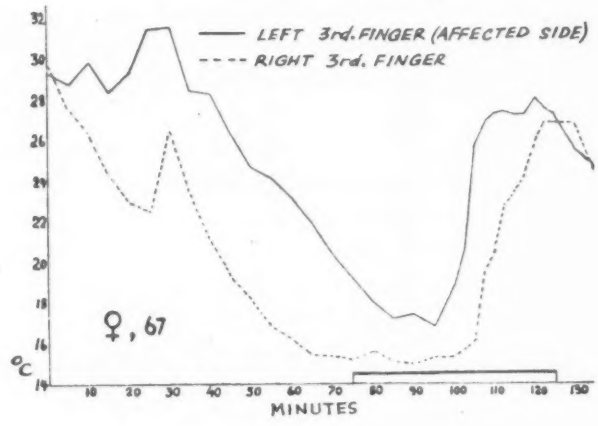
During the decrease in temperature a few " peaks " also occurred on the curve representing the affected side (most marked in Figs 4 and 5), indicating

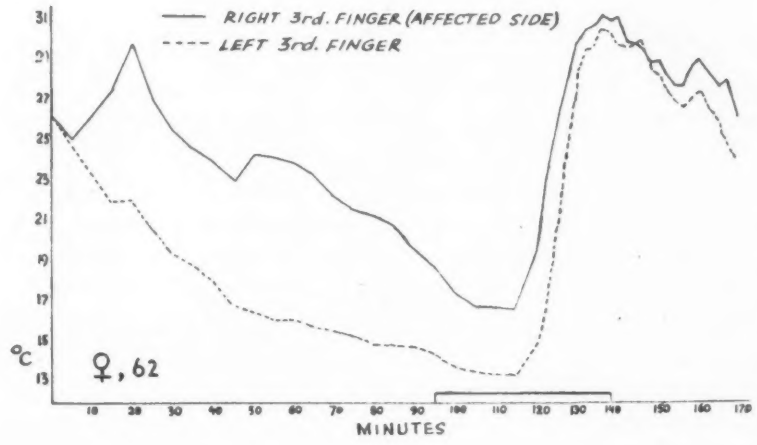


FIGS 4 and 5.—Higher temperature on *affected* side with slight flushes.



FIGS 6, 7, 8.—Higher temperature on *affected* side.





small unilateral "flushes" on the affected side. These "peaks" are of almost the same height and duration as those occurring with menopausal flushes.

In a few cases the increase in temperature occurred considerably earlier on the affected than on the healthy side (Figs 6, 7, 8). The most marked time difference will be seen in Fig. 6, in which the increase occurred $7\frac{1}{2}$ minutes later on the healthy than on the affected side.

As a rule the maximum increase in temperature reached approximately the same level on both sides. In Fig. 5, however, it may be seen that the affected side reached a level 3° higher than the healthy side.

Fig. 9 shows an equal decrease in temperature and a simultaneous increase, during which, however, there was a rather marked difference between the two sides, the affected side being lower than the healthy one.

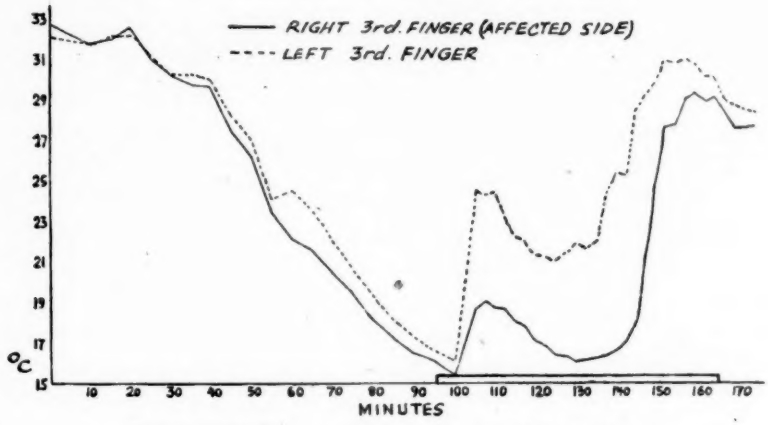


FIG. 9.—Higher temperature on *unaffected* side.

We may now ask the question: Are these curves expressions of unilateral vegetative disturbance or merely of a variation within physiological limits?

Of course, it would have been best to have studied an equally large number of normal patients. I did not, however, consider this necessary, feeling justified in using Vanggaard's experimental results from a normal series as a basis for comparison, since his method is in principle the same as the present one.

Vanggaard's cold box was designed somewhat differently from mine. This is not important, if only the cold box fulfils the necessary conditions. Irradiation of heat from the warmer arm to the colder one cannot take place, since measurements have shown the air between the arms to be of the same temperature as that in the remaining parts of the box.

Vanggaard used fixed thermo-elements, but I used a mobile one; in my experience this does not cause any error worth mentioning in measurements on the fingers where the subcutaneous tissue is so scanty that a major or minor pressure during the measurements gives the same result.

Vanggaard's normal series comprised thirty subjects. In 26 of these he found the curves to be closely symmetrical with regard to the rhythm of their movements, and the absolute values of skin temperature to be close to each other. In the other four instances, however, he found that after the heating was stopped the skin temperature fell much more quickly on one side. Before the heating, on the other hand, the decrease in temperature did not show divergences of more than 2 or 3°.

In other words, it is reasonable to presume that marked differences in temperature during the first falling part of the curve may be interpreted as an expression of abnormal vegetative impulses on one side. Of course, it is not possible to tell from the curves alone which side is affected, but one may assume that the curve from the side affected by peri-arthritis stands for the abnormal findings.

Thus, the decrease in temperature after discontinuation of heating may present rather marked physiological variations on the two sides. Therefore, and also because at this stage the experiment had often already lasted for about 3 or 4 hours, I did not trace the decrease in temperature for a long time in this phase.

According to Vanggaard, the time at which the temperature begins to increase on the two sides is also subject to physiological variations, and may be up to 8 min. later on one side than the other. This occurred in only one of my cases, and in the others the interval amounted to only a few minutes.

On the basis of these observations, I consider Curves 4 to 8 to be abnormal. Curve 9 is probably not abnormal, since the decrease in temperature was equal. The difference between the two sides was not seen until the increase began and the temperature then rose further on the healthy side.

This prompts the question whether the case histories of the five patients represented in Curves 4 to 8 differ from those of the other patients without trophic disturbances. To elucidate this question the case histories of the five patients with abnormal curves are given in some detail, and the findings in the remaining cases are summarized very briefly.

Case Reports

Curve 4, female, aged 56. She had previously been on the whole healthy. Menopause occurred 7 years ago, but she had still hot flushes. She had been treated for a long time with phenobarbitone and stilboestrol, when the shoulder lesion set in.

Present Illness.—Gradually increasing pain in right back of the head, shoulder, and arm; paraesthesia in the thumb and two radial fingers, no temperature sensations, no stiffness of the fingers, no injury. Marked limitation of motion. Duration of disease 8 months, skin temperature measured 5 months after onset. *X* ray of right shoulder showed nothing abnormal. Wassermann reaction negative, gonococcal complement-fixation test negative, antistreptolysin titre 22, Hb 108 per cent., erythrocyte sedimentation rate 22—30—28—26. She had received physical therapy for $2\frac{1}{2}$ months with little effect, and *x*-ray therapy for 3 months, as a result of which she had been relieved of pain.

Curve 5, female, aged 59. Five years previously she had had right-sided peri-arthritis of the shoulder which yielded in the course of 3 months to *x*-ray therapy, and had otherwise been healthy on the whole. Menopause occurred 11 years previously; at the outset she had had hot flushes, but not during recent years.

Present Illness.—Gradually increasing severe pain in the left shoulder and arm, no paraesthesia, no temperature sensations, no stiffness of the fingers, no injury, no phenobarbitone. Severe limitation of motion. Duration of disease 6 months, skin temperature measured 2 months after onset. *X* ray of left shoulder showed nothing abnormal. Wassermann reaction negative, gonococcal complement-fixation test negative, antistreptolysin titre 64, Hb 89 per cent., erythrocyte sedimentation rate 4—20—22—6. She had received physical therapy for 6 weeks with little effect, and *x*-ray therapy for 3 months, as a result of which she had been relieved of pain.

Curve 6, female, aged 48. She had previously been healthy, but had always been " nervy " and moody. Menstruation regular, no hot flushes.

Present Illness.—Acute onset of pain in right shoulder and arm, paraesthesia in all fingers and thumb, no stiffness of the fingers, no injury, had received phenobarbitone.

Marked limitation, particularly of active motion. Appeared to be exaggerating her symptoms. Duration of disease 3 months, skin temperature measured 8 days after onset, when she had had a sensation of heat in the right upper arm for 2 days; this subsided 4 or 5 days after the experiment. *X* rays of right shoulder showed nothing abnormal, of cervical column showed spondylitis deformans of C5, C6, and C7. Wassermann reaction negative, gonococcal complement-fixation test negative, Hb 90 per cent., erythrocyte sedimentation rate 7. She had received physical therapy for 3 months, and as a result was almost free from pain.

Curve 7, female, aged 67. Long-standing asthma for which she had periodically taken ephedrine. Menopause occurred 20 years ago, with hot flushes at the outset, but none at present.

Present Illness.—Gradually increasing, but not particularly severe, pain in left shoulder and arm, paraesthesia, stiffness, and slight swelling of the fingers of the left hand, particularly in the morning, no temperature sensations, no injury, no phenobarbitone. Moderate limitation of motion, left-sided Dupuytren's contracture, no hilodermia, no trophic skin disturbances, especially nothing suggesting reflex dystrophy. Duration of disease 6 months, skin temperature measured 5 months after onset. *X* rays of shoulders and hands showed nothing abnormal, particularly no halisteresis, lungs showed sequelae of right-sided interlobar pleurisy. Electrocardiogram showed nothing abnormal. Wassermann reaction negative, gonococcal complement-fixation test negative, antistreptolysin titre 80, Hb 90 per cent., erythrocyte sedimentation rate 23—40. She had received physical therapy for one month, and as a result was almost relieved of pain. Dupuytren unchanged.

Curve 8, female, aged 62. Had always been somewhat nervous, but otherwise healthy. Menopause occurred 15 years previously, and she still had periodical hot flushes.

Present Illness.—Gradual onset with a sensation of chill at the back of the head, increasing pain in the right shoulder and arm and two ulnar fingers, no paraesthesia, no stiffness of the fingers, no injury, had received phenobarbitone. Slight limitation of motion; movements of cervical column somewhat restricted. Duration of disease 7 months, skin temperature measured 2 months after onset. *X* rays of right shoulder showed nothing abnormal. *X* rays of cervical column showed spondylitis deformans. Wassermann reaction negative, gonococcal complement-fixation test negative, antistreptolysin titre 40, Hb 95 per cent., erythrocyte sedimentation rate 12—15. She had received physical therapy for 3 months with little effect, and then *x*-ray therapy for 3 months with good effect, but still suffered from mild pains.

Observations on Five Abnormal Cases

(1) Only two patients had temperature sensations, one at the back of the head, and the other in the upper arm, but no such sensations had occurred in the hands. This finding, however, does not rule out the occurrence of abnormal vegetative impulses at this site, as I have a few times recorded temperature differences of 7-8° without the patients having noticed a difference on the two sides. As a rule the patients themselves notice the difference, but at other times patients may report a difference, although the measurements show exactly the same temperature, so that subjective statements are of doubtful value.

(2) All the patients had radiating pain and three had paraesthesia in the fingers.

(3) One patient exhibited Dupuytren's contracture, but no other trophic disturbances.

(4) In three cases the lesion was right-sided and in two left-sided, but the course of the curves was found to be independent of the side affected.

(5) The duration of the disease had been fairly long in all cases and had proved rather refractory to treatment which in three cases had had to be supplemented by *x*-radiation.

(6) Two patients exhibited spondylitis deformans of the cervical vertebrae. It must be stated, however, that only those patients who showed restricted mobility of the cervical column were *x*-rayed from this point of view. Opinions are divided as to the significance of this finding; among fourteen patients with rheumatic pain in the region of the shoulder and trophic disturbances of the hands, Oppenheimer found spondylitis deformans of the cervical vertebrae in each case, whereas this phenomenon was observed only in exceptional cases by Steinbrocker who does not attribute much importance to it.

(7) The sedimentation rate was slightly enhanced in most cases.

(8) Two patients suffered from menopausal hot flushes.

Observations on 21 Normal Cases

Symptoms.—Nervous, five; menopausal hot flushes, three; gradual onset, twelve; acute onset, six traumatic and three non-traumatic; temperature sensations, one patient (" chill " at the back of the head); stiffness of fingers, one; paraesthesia, eight; radiation of pain, seventeen; spondylitis of cervical vertebrae, three; peri-articular calcifications, three; raised erythrocyte sedimentation rate, six.

Duration of Disease.—This ranged from 1 month to several years, the patients being fairly equally distributed between these two extremes. The time at which the temperature was measured varied also, with the extremes at a fortnight and several years after the onset. In the majority of cases, however, the measurement took place after the disease had lasted for 3 to 5 months and usually 2 months before treatment was discontinued.

Therapy.—Two had previously received *x*-ray therapy, both with no improvement worth mentioning. Three were referred for *x*-radiation because physical therapy had failed.

B. Cases with Trophic Disturbances (3)

Two cases of bilateral shoulder-hand syndrome were included to find if there was any difference of degree between the two sides. In both the curves fell and rose again equally.

The third case, one of typical right-sided shoulder-hand syndrome, had arisen after a " wrong " movement performed by the patient in picking something up from the floor. At the time of examination the disease had persisted for 6 months; the patient was improving on ordinary physical therapy, and one month after examination the pain had virtually disappeared. In other words, one would expect the curve to correspond to the findings during the healing phase, and this it did (see Fig. 10). The difference in temperature between the two sides was not particularly marked, but the increase on the affected side occurred a few minutes later, a sign of

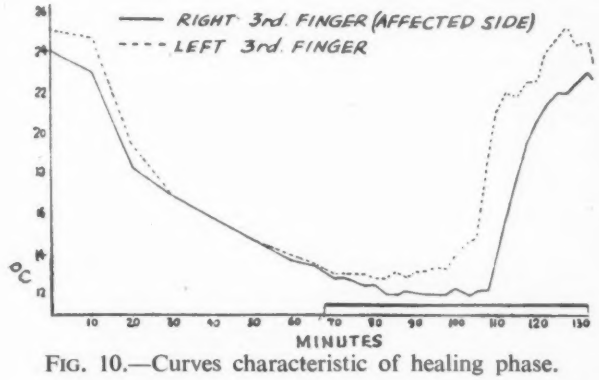


FIG. 10.—Curves characteristic of healing phase.

vasospasms. While the disease was in the active stage, the patient had complained of a sensation of heat in the hand, but she was not examined during this phase, as I did not then possess the necessary apparatus.

Discussion

It is evident from these data that striking, let alone constant, differences were not observed between patients with normal curves and patients exhibiting differences in temperature on the two sides during cooling.

To evaluate the findings of the vegetative studies in patients without trophic disturbances, it would be reasonable to make a comparison with findings in patients with trophic disturbances of the fingers. As my own series is rather inadequate in this respect, I shall also report the results of others.

As emphasized by Steinbrocker and others (1948), the shoulder-hand syndrome belongs to the group of diseases ordinarily named " reflex dystrophies ", a term which refers in the main to the characteristic vasomotor and trophic disturbances accompanying these conditions. The term " shoulder-hand syndrome " refers merely to the peculiar localization of the changes.

It is generally agreed that reflex dystrophies run through certain phases with varying vegetative disturbances. According to Steinbrocker and others (1948), the shoulder-hand syndrome has three different phases, corresponding in principle to the phases of reflex dystrophy, regardless of site.

Haldbo (1942) surveyed the vegetative disturbances in two phases, elucidated by tests of vegetative function. Since his procedure was the same as mine, it seems reasonable to use his experimental results as a basis for comparison. In the first or developmental stage—characterized by severe oedema, pain, and restriction of movement—there are always disturbances referable to paralysis of the sympathetic nerves, i.e. hyperaemia and anhidrosis. Correspondingly, Haldbo observed slower and less complete cooling of the affected than of the unaffected side. In the second or healing stage—characterized by tissue atrophy—arteriospasms manifest themselves in a greater decrease and a slower increase of skin temperature on the affected side. The affected side also exhibits hyperhidrosis. Both findings indicate increased sympathicotonia.

I can see no essential difference between Steinbrocker's Phases 2 and 3, which are both stages of healing, and his description of the shoulder-hand syndrome may thus be said to correspond to Haldbo's observations on reflex dystrophies in general, especially since several of Haldbo's cases belong, in fact, to the shoulder-hand syndrome group.

The findings in the present study correspond in principle to the experimental results found during the development of reflex dystrophy. Not one of my five abnormal cases, however, showed trophic disturbances at any time, so that the condition is probably interpretable as an abortive shoulder-hand syndrome, which infers the presence of abnormal vegetative impulses in the fingers of the affected side without manifest trophic disturbances.

Arteriospasms did not occur on the affected side. This is due either to chance,

or to the fact that any arteriospasms were so slight as to be undemonstrable by the method used. A third possibility—and probably the most likely one—is that vasospasms do not occur until the time when the patients are recovering. In this respect I have made the regrettable error of not following-up the patients by repeated measurements of skin temperature.

Abnormal vegetative impulses without trophic disturbances occurring after injury were described by Leriche (1923), who found by oscillometric experiments that any injury to a limb, open or closed, is followed by vasomotor disturbances; at the outset these take the form of vasoconstriction, but this usually changes to dilatation which may persist for a few months without clinical manifestations. These phenomena do not appear to have been studied previously in ordinary peri-arthritis of the shoulder without trophic disturbances.

The pathogenesis of reflex dystrophies, and thus also of the shoulder-hand syndrome, is obscure. Ordinarily Steinbrocker's explanation is accepted:

> Impulses causing the trophic and vasomotor disturbances issue from a focus of irritation through an axone reflex or by antidromal stimulation of sensory autonomic nerves. The focus of irritation may be an area of damaged tissue (trauma), the heart (angina pectoris), or the central vegetative centres (cerebral haemorrhage). A reflex genesis is considered most likely because interruption of the efferent pathway in the reflex arc (blocking of the sympathetic ganglia) seems to improve the condition.

In the present writer's opinion, the following objections may be raised:

(1) Sympathetic blocking produces no convincing effect in these conditions. If the blocking did affect an essential factor of the disease, the therapeutic result would be far more striking. Jespersen's results have been reported above. As to Steinbrocker's results, the blocking failed in some cases, and in most instances the changes persisted for years regardless of blocking or sympathectomy. The idea of blocking the sympathetic ganglia in these conditions also appears paradoxical, since vasomotor tests have shown that the developmental stage is marked by reduced sympathetic function, manifesting itself as an abnormally increased hyperaemia, which would only be further increased by sympathetic blocking. This is pointed out by Steinbrocker as well as by Haldbo, but both workers find it important first to interrupt the presumed reflex mechanism.

(2) If the idea of a reflex be disregarded, it would appear more logical to try the opposite procedure, viz. to reproduce the vasospasms encountered in the healing phase. This has seemingly not been tried, presumably because of the great practical difficulties. A possible procedure might be iontophoresis of an adrenergic substance. A reflex mechanism is almost certainly indispensable to start the process, but at a later stage the essential factor is probably damage to the vegetative nerve centres. Such damage was found by Sunder-Plassmann in the form of degenerative processes in the ganglion cells of sympathetic trunks from patients suffering from these conditions.

Summary

In five out of 27 patients with peri-arthritis of the shoulder, measurements of the skin temperature revealed abnormal vegetative impulses in the fingers of the affected side despite the absence of trophic disturbances. This must be interpreted as a condition which might be called an abortive shoulder-hand syndrome, the pathogenesis of which is probably analogous with that of a manifest shoulder-hand syndrome, i.e. a result of vegetative disturbance.

The experimental results support the idea that peri-arthritis of the shoulder may, in some cases at least, result from disturbances in the vegetative nervous system.

My thanks are due to the National Danish Association against Rheumatic Diseases for financial assistance in these experiments.

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Périarthrite scapulaire—Étude de la fonction végétative

RÉSUMÉ

Chez cinq sur 27 malades atteints de périarthrite scapulaire la mesure de la température cutanée montra l'existence des impulsions végétatives anormales dans les doigts du coté atteint, malgré l'absence de troubles trophiques. Ceci doit être interprêté comme indiquant une affection qu'on pourrait appeller " syndrome scapulo-manual abortif ", et sa pathogénie est probablement analogue à celle du syndrome scapulo-manual manifeste, c'est à dire une conséquence d'un trouble végétatif.

Les résultats expérimentaux viennent a l'appui des théories selon lesquelles la périarthrite scapulaire pourrait, dans certains cas tout au moins, dériver des troubles du système nerveux végétatif.

Periartritis escapular—Estudio de la función vegetativa

SUMARIO

En cinco de los 27 enfermos con periartritis escapular la determinación de la temperatura cutánea mostró la existencia de impulsos vegetativos anormales en los dedos del lado afectado, a pesar de la ausencia de disturbios tróficos. Al interpretar este hecho se llega a la conclusión de que se trata de una afección que merecería el nombre de "síndrome escapulo-manual abortivo", y su génesis es probablemente análoga a lá del síndrome escápulo-manual manifesto, es decir el resultado de un disturbio vegetativo.

Los resultados experimentales sostienen las teorias según las cuales la periartritis escapular puede, en ciertos casos por lo menos, resultar de los disturbios del sistema nervioso vegetativo.

LATE RESULTS OF GOLD TREATMENT IN RHEUMATOID ARTHRITIS

BY

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Gold treatment has always been a matter of debate; this is partly owing to the difficulties in judging the results, and partly owing to toxic secondary effects. The tendency of rheumatoid arthritis to spontaneous remissions and progressions has not been sufficiently taken into account. In addition, the various case histories are not comparable, since they fail to give elementary information concerning the age-distribution, sex, duration of history, etc. Several authors define the terms "healed, improved, unchanged, and deteriorated" more or less subjectively. Steinbrocker and Blazer (1946) proposed giving points according to the clinical findings to obtain a more objective conception of the effect of this therapy. Generally, most of the published material lacks control groups for the comparison of gold treatment on the one hand, and, e.g., physical treatment only, on the other.

Most authors give only the primary results of treatment, the number of improved cases varying between 50 and 95 per cent. Such a high percentage of improved cases as 95 per cent. is, apparently, due to the inclusion of the mild cases with uncertain diagnosis. As to the late results of this therapy, the figures are much less encouraging. Thus, Ragan and Tyson (1946) showed that in a series of 142 patients, 75 per cent. relapsed in the course of 3 years. Kling, Vento, and Sashin (1949) found that 17 per cent. relapsed in a series of 455 patients after one year, 57 per cent. after 5 years, and 75 per cent. after 10 years.

As stated above, most of the reports lack control groups. Nevertheless, some investigations deal with such groups. Ellman, Lawrence, and Thorold (1940) and Fraser (1945) found that after one year of observation the cases treated with gold showed better results than those not so treated. Secher (1946), after a control examination held 5 to 13 years later on 231 cases of rheumatoid arthritis treated with sanocrysin, showed that 60 to 70 per cent. had improved. Snorrason (1950), partly on the same number of cases, demonstrated an improvement in 80 per cent. after 4 years' follow-up. In a control group given only physical therapy, he obtained only a 50 per cent. improvement. Short, Beckman, and Bauer (1946) declared gold treatment to be of no definite value, but their experience of it was limited to 47 patients. Waine, Baker, and Mettier (1947) published a control examination of 120 patients, 62 of whom had been treated physically and 58 with gold, with doses exceeding 0·5 g. per patient. The cases were followed up for an average of 2·9 years and the percentage of those free from symptoms, or markedly

improved, was 56·9 for those treated with gold and 29·1 for those treated only physically.

Present Investigation

In the period from the summer of 1949 to May, 1950, 210 cases of rheumatoid arthritis, treated at the Åsö Hospital and Södersjukhuset in the years 1934 to 1945, were subjected to follow-up examination. All those who had received less than 0·8 g. gold at the first treatment were excluded. Below, the composition of the material and the results of the treatment are set down in tabular form.

TABLE I
PRIMARY MATERIAL

Sex	Male	Female	Total
Summoned for examination	109	214	323
Examined	72	138	210
Deceased	15	32	47
Unknown address	2	6	8
Failed to attend	20	38	58

Table I shows that 323 patients were asked by letter to submit to a follow-up examination, and that 210 were examined. This reduction by 113 cases was due to the fact that 47 had died and 66 did not attend for other reasons. The investigation involved sending a questionnaire to the 323 patients constituting the primary material. The following questions were to be answered:

Have you still any trouble in the joints and, if so, will you state the degree of severity ?
Have you received any subsequent treatment ?
Have you received gold treatment again and, if so, with what result ?
Are you willing to attend a control examination ?

The patients who attended were all subjected to a control examination. Besides the usual somatic examination including joint status, the sedimentation rate was noted, and the blood tested. On the basis of previous records and examination findings filed in our card index, the different patients were classified as shown in Table II.

TABLE II
RESULTS AFTER 5 YEARS OR MORE, BY SEX

Class	Male		Female	
	No.	%	No.	%
No symptoms	20	28	12	9
Improved	22	31	42	30
Unchanged	11	15	23	17
Deteriorated	17	26	61	44

Table II shows the results of treatment after 5 years or more. The material was divided by sex, and a marked difference was found between the sexes as regards

the results of this treatment. On the basis of the total material, the symptom-free group—which was, moreover, the only one with a preponderance of males—showed that 28 per cent. males and 9 per cent. females were free from symptoms. The next two groups " improved " and " unchanged " display no great variation between the sexes. Only 26 per cent. of the total number of males were found to have deteriorated, whereas the corresponding figure for females was as high as 44 per cent. These figures are in fair agreement with the general conception that rheumatoid arthritis affects the female sex the most severely.

TABLE III

INITIAL IMPROVEMENT (%)

Male	Female	Total
75	80	78

Table III shows that quite different figures were obtained concerning the immediate effects of the initial gold treatment. These figures clearly demonstrate that it is impossible to arrive at any judgment of the long-term prognosis merely by reference to the initial effects.

TABLE IV

RESULTS OF TREATMENT BY TIME SINCE ONSET (%)

No. of Years	Symptom-Free	Improved	Unchanged	Deteriorated
<1	56	37	44	26
1	22	14	15	21
2-5	13	25	32	38
>5	9	24	9	15

Table IV shows, in our opinion, an important principle for gold treatment. It has been ascertained by means of animal experiments that an early administration of gold treatment has a more favourable effect than that obtained if the treatment is started at a later stage of the disease. In the course of years, we have arrived at the same conclusion, and our investigation points in the same direction. Table IV illustrates how the late effect is influenced by the lapse of time between the onset of the disease and the beginning of the gold treatment. It was found that in the symptom-free group as many as 56 per cent. were treated with gold within a year of the onset. In the other groups the results in cases treated with gold before the termination of one year were 37 per cent. improved, 44 unchanged, and 26 deteriorated. The corresponding figures in the various groups of those treated with gold after the elapse of one year do not show the same preponderance in the symptom-free group, and this also applies to the remaining cases treated with gold

at a later stage. Though the material is limited, in comparing the groups of symptom-free and deteriorated cases, the figures of 56 and 26 per cent. may be said to be significant.

In the different groups of results, the length of time elapsing between the first and second gold treatment was also investigated. It was found that in the more successful cases the second gold treatment had been given a shorter time after the first treatment than in the less successful cases.

Obviously, against these figures and the conclusions drawn from them, the objection may be raised that the patients who are now free from symptoms were of the mild type to begin with, and that their disease would probably have been healed without treatment. In a study of records made at the time of the first gold treatment, based on articular findings, sedimentation rate, serologic titres, etc., the cases were classified as mild, medium-severe, and severe. This classification was not made according to Steinbrocker (1946), but should at any rate give some idea of the material.

Considering the whole series of patients on the basis of this distribution in regard to severity, we did not find that the relation between mild, medium-severe, and severe cases varied sufficiently in the different groups to have influenced the early effects of the gold or the late results.

The different sexes have already been demonstrated as manifesting a different prognosis. Another fact of interest is the age of the patient at the onset of disease. In an analysis of the material, a comparison between the more and less successful from a therapeutic point of view showed that the former had more often fallen ill at a younger age. Using the division into groups of " free from symptoms ", " improved ", " unchanged ", and " deteriorated ", it will be found that 41 per cent. of the patients who were free from symptoms at the follow-up examination had fallen ill before the age of 30. The corresponding figures for the groups " improved ", " unchanged ", and " deteriorated ", were 27, 26·5, and 14 per cent. Similar figures are obtained when 40 years is set as the upper limit. 66 per cent. of the cases free from symptoms fell ill before that age, and in the groups " improved ", " unchanged ", and " deteriorated ", the corresponding figures are 48, 44, and 38 per cent. Although the differences are insignificant and the cases not numerous, the figures obtained indicate that the earlier onset of the disease involves a somewhat more favourable prognosis.

Yet another factor which might be supposed to influence the course of the disease is the type of attack. Egelius, Hävermark, and Jonsson (1948) published an investigation of early symptoms in rheumatoid arthritis in which the classic onset (viz. stealthy beginning, slowly progressive course, no fever, and symmetric joint symptoms starting in the small joints and progressing centripetally) was demonstrated as being not nearly so common as had been assumed. Compared with more acute or atypical forms of attack, the classic type described above would rather have been expected to prove less favourable as regards the prognosis. The present material has been studied from this particular point of view without yielding any evidence of this.

From our present endocrinological standpoint, ACTH and cortisone cannot as yet be relied upon to offer any really conclusive cure, and gold treatment must still be considered as the best, though by no means an ideal, procedure. If gold must be used, it is apparently desirable to start the treatment at an early stage; the first course of treatment should be followed, after a short period, preferably 2, 3, or 4 months as stated above, by a fresh course of treatment, or else after the first treatment a maintenance dose should be administered. It has been observed that the gold is all excreted in up to 7-12 months from the discontinuation of the therapy. It would seem important, therefore, to maintain a certain threshold value of the gold in the tissues so as to prevent the disease from breaking out again. The action of gold is unknown. Various theories have been advanced regarding a bacteriostatic action, enzyme inhibition, etc. It is possible that the effect of the gold is an action on the pituitary and adrenal cortex. Attempts have been made to combine gold treatment with ACTH or cortisone administration in order to obtain a better and more protracted effect. Hitherto, however, our experience of this combined therapy has not been encouraging.

As a practical outcome of the present investigation, the initial course of gold treatment is now followed on a larger scale at the Rheumatic Dispensary of Södersjukhuset (South Hospital) by administering small maintenance doses every other, or every third, week *ad modum* Freyberg (1942).

Summary

Follow-up examinations were made of 210 rheumatoid arthritis patients (two-thirds of whom were females), 5 to 15 years after gold treatment. The following conclusions were drawn:

(1) It is not possible from an initial improvement to obtain an idea of the later prognosis.

(2) Judging from our material, the male has a distinctly more favourable prognosis.

Of the males, 28 per cent. were "symptom-free", 31 per cent. "improved", 15 per cent. "unchanged", and 26 per cent. "deteriorated".

Of the females only 9 per cent. were "symptom-free", 30 per cent. "improved", 17 per cent. "unchanged", and as many as 44 per cent. "deteriorated".

The symptom-free group comprised 15 per cent. of all cases, this figure agreeing well with results obtained by other investigators, whose figures as a rule lie between 10 and 15 per cent. A further 30 per cent. of the total were improved. Thus, the symptom-free and improved groups together represent 45 per cent. of the whole number, and 38 per cent. were found to have deteriorated.

(3) Patients who contract the disease at an early age have a better prognosis than those who acquire it at a later age.

(4) It appears important that gold therapy should be introduced at an early stage. Cases in which the gold treatment was begun a year after the start of the disease showed much better results than those in which it was begun later.

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Résultats éloignés du traitement de l'arthrite rhumatismale par des sels d'or

RÉSUMÉ

On a examiné des malades (dont deux tiers étaient des femmes) atteints d'arthrite rhumatismale 5 à 15 ans après le traitement par des sels d'or. On arriva à des conclusions suivantes:

(1) Une amélioration initiale n'offre aucune indication pronostique ultérieure.

(2) D'après le matériel étudié, le pronostic chez les hommes est nettement plus favorable. Parmi les hommes, 28% étaient "sans symptômes", 31% " améliores ", 15% " sans changement ", et 26% " empirés ".

Parmi les femmes, 9% seulement étaient " sans symptômes ", 30% " améliorées ", 17% " sans changement ", et jusqu'à 44% " empirées ".

Le groupe de " sans symptômes " représentait 15% du chiffre total, ce qui concorde avec les résultats des autres auteurs, dont les chiffres, en général, varient entre 10 et 15 pour cent. Avec un pourcentage total de 30% d' " améliorés ", on arrive à 45% des résultats favorables. Dans 38% des cas la santé des malades s'était aggravé.

(3) Le pronostique de ceux qui contractent la maladie à un âge préccoe set meilleur que celui des rhumatisants au début tardif.

(4) Il parait important qu'on commence le traitement par des sels d'or de bonne heure. Des cas où ce traitement avait commencé un an après le début de la maladie présentent de meilleurs résultats que ceux traités plus tard.

Resultados tardíos de la auroterapia de la artritis reumatoide

SUMARIO

Enfermos con artritis reumatoide (dos terceras del sexo femenino) fueron examinados de cinco a quince años después del tratamiento con sales de oro. Se llegó a las conclusiones siguientes:

(1) Una mejoría inicial no ofrece indicación alguna respecto al pronóstico ulterior.

(2) Basándose en el material entero, el pronóstico para los hombres es netamente más favorable. El 28% de los hombres estaban " sin síntomas ", el 31% " mejorados ", el 15% " sin cambiar ", y el 26% " empeorados ".

Respectó a las mujeres, el 9% sólo estaban " sin síntomas ", el 30% " mejoradas ", el 17% " sin cambiar ", y hasta el 44% " empeoradas ".

El grupo de " sin síntomas " comprendía el 15% del total de los casos, lo que corresponde a los resultados obtenidos por otros investigadores, cuyas cifras oscilan generalmente entre el 10 y el 15 por ciento. El 30% del total pertenecía al grupo de los " mejorados ", que con el previo grupo forman el 45% de resultados favorables. El 38% del total había empeorado.

(4) Enfermos que contraen la enfermedad a una edad temprana tienen el pronóstico mejor que los demás.

(5) El tratamiento precoz con sales de oro parece ser importante; en casos en que éste fué empezado un año después del principio de la enfermedad se obtuvo mejores resultados que en los en que fué instituido más tarde.

CREATINE METABOLISM IN ARTHRITIS

BY

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The results published by Granirer (1949) of his investigation of creatinuria in patients with rheumatoid arthritis and osteo-arthritis appeared especially interesting, as few such studies had previously been recorded.

The extensive work of Wang (1939) on creatine metabolism included a study of only three arthritic patients. All of these were regarded as having significant creatinuria of varying degree, but this was attributed by Wang to the accompanying muscular atrophy. Pemberton and Buckman (1920) had earlier studied forty cases of arthritis in men, with the conclusion that about one-half of these showed an abnormally high value for blood "creatine", but that only three of the cases showed creatinuria. In the control series of nine normal men, no creatinuria was found.

Granirer's results were obtained from adult male and female subjects and yielded the following mean values for the 24-hr urinary creatine excretion:

675 mg. for ten osteo-arthritics
185 mg. for ten elderly healthy controls
176 mg. for ten patients with rheumatoid arthritis
161 mg. for ten young healthy controls.

These findings, together with a consideration of normal levels of creatinuria previously postulated by certain other workers, led Granirer to conclude that creatinuria is a normal process in the adult male and female; that patients with active rheumatoid arthritis have also a normal creatinuria; and that in patients with osteo-arthritis there exists the possibility of an abnormal excretion of creatine.

It is well known that creatine is an integral factor in the activity of muscle and in the cycle of carbohydrate metabolism, although the amount of creatine excreted in the urine depends rather on a process of disposal of creatine present in excess of that required for metabolic needs. The nature and purpose of the process of disposal of the excess creatine are still obscure (Peters and Van Slyke, 1946), though it has been noted by various investigators (quoted by Boland, 1950) that a marked increase in creatinuria was found during the early phase of cortisone and ACTH administration, which increase may or may not continue during the period of treatment.

Using an improved method (Peters, 1942) for the determination of creatine

in blood plasma and in urine, various workers (see Peters and Van Slyke, 1946) have shown that the concentration of creatine in blood plasma is normally low, being usually below about 0·6 mg. per 100 ml. plasma in adult males, though frequently somewhat higher in adult females. The normal low levels do not give rise to creatinuria, the appearance of which is dependent upon plasma concentrations in excess of the critical value above mentioned. Hence, it is to be expected that the urine of normal adult males and of the majority of normal adult females will contain no creatine.

This has been confirmed by Maw (1947), who demonstrated the absence of creatinuria in a group of normal young men and in about half of a group of normal young women. When present in the females, the creatine excretion was generally about 50 mg. per day, though occasional values up to 150 mg. per day were noted.

A recent investigation of the creatine excretion of male patients with fibrositis by Sylvest and Hvid-Hansen (1950) has also yielded supporting evidence. Out of 38 patients, they found that thirty had no creatinuria and that two healthy control men likewise showed no excretion of creatine.

The finding by Granirer (1949) of substantial creatinuria in twenty healthy control subjects as well as in twenty patients with arthritis therefore requires explanation. It seems probable that the results depended on the use for the determination of urinary creatine of the analytical method of Folin (1914), a method based on the classical reaction of Jaffe, which is well known to lack specificity. In this connection, it may be noted that Peters and Van Slyke (1946) ascribed the finding by certain earlier workers of high levels of creatine excretion in normal men to analytical errors. Nevertheless, the markedly *greater degree* of creatinuria shown by all of the ten patients with osteo-arthritis in Granirer's series still appears to represent an abnormality characteristic of this condition.

We have therefore investigated the incidence and degree of creatinuria in groups of male and female patients with rheumatoid arthritis and osteo-arthritis, and have also determined the plasma creatine levels coincidentally, in an attempt to define more clearly the possibility of abnormal creatine metabolism in arthritis.

Patients Studied

The patients in our series were selected from those coming to Highfield Hospital for the customary course of Spa treatment. The specimens were taken before this treatment was begun, although all the patients had had some form of physiotherapy at some time previously. They were all ambulant and receiving the usual hospital diet which was regarded as having a negligible influence on creatine metabolism.

Only those patients who could be classified in the broad groups of rheumatoid arthritis and osteo- (or degenerative) arthritis, and who also had minimal soft tissue involvement, were selected for study.

In the series of 68 patients (40 women and 28 men), 33 suffered from rheumatoid arthritis and 35 from osteo-arthritis. Their ages varied from 21 to 61 years, but only seven were under 40 years. The duration of disease from the onset of symptoms varied in the rheumatoid group from 6 months to 17 years and in the osteo-arthritic group from one to 22 years. None had any neurological involvement, nor did any suffer from thyrotoxicosis, myxoedema, diabetes, or pituitary disturbance.

Analytical Methods

Each subject collected the 12-hr urine from 8 p.m. to 8 a.m. The relatively concentrated night-urine specimens were chosen in order to increase analytical sensitivity and to minimize any possible effect of exercise on the excretion of creatine. Although Maw (1947) has shown that creatinuria is not related to any phase of the menstrual cycle, the collection of specimens coinciding with the menstrual period was avoided. The absence of proteinuria was noted in every case. The urinary volume was measured, the creatine concentration recorded in mg. per 100 ml., and the content recorded in mg. per 12-hr night urine. Each plasma sample was obtained from oxalated blood, collected at about 10 a.m. after the period of urine collection, and the creatine concentration was recorded in mg. per 100 ml. plasma.

The colorimetric reaction of Jaffe in the refined (photelometric) form described by Peters (1942) was used for the determination of creatine in both plasma and urine. This method was claimed by Peters to yield reliable values, and his claim has been substantiated by Allinson (1945) using a specific enzymatic method. It should be noted that Peters's procedure is not applicable to the analysis of whole blood, as erythrocytes contain chromogenic material other than creatine.

Results and Conclusions

Table I summarizes the analytical results derived from the plasma and urine samples of forty female and 28 male patients respectively. Regarding the results for plasma creatine, it is noteworthy that for female patients, only one value in each of the disease groups exceeded the upper limit of normality (0·9 mg. per 100 ml. plasma); whereas for male patients, four values out of fourteen in each of the disease groups exceeded the upper limit of normality (0·6 mg. per 100 ml. plasma).

TABLE I

ANALYTICAL DATA FOR 40 FEMALE AND 28 MALE PATIENTS

Creatine Component Estimated	Rheumatoid Arthritis			Osteo-Arthritis			Statistical Evaluation of the Difference between the Means	
	Range of Values Found*	Mean Value	S.D.	Range of Values Found*	Mean Value	S.D.	*t*	*P*
40 *Female Patients*								
Plasma creatine (mg. per 100 ml.)	0·13-1·00	0·51	0·25	0·29-0·89 (1·00)	0·52	0·21	0·14	0·9
Urine creatine (mg. per 100 ml.)	0-22 (27)	8	9	0-23 (44)	8	11	—	—
Urine creatine (mg. per 12-hr night urine) ..	0-84	26	42	0-126 (158)	36	47	0·70	0·5
28 *Male Patients*								
Plasma creatine (mg. per 100 ml.)	0·13-0·87 (1·09)	0·44	0·30	0·16-0·90	0·51	0·22	0·70	0·5
Urine creatine (mg. per 100 ml.)	0-17 (41)	8	12	0-6 (27)	3	7	1·35	0·2
Urine creatine (mg. per 12-hr night urine) ..	0-79 (144)	32	42	0-24 (103)	11	28	1·52	0·1

* A single value, where it exceeded the mean +2 S.D., is set out in brackets after the general range of values.

Calculated mean values with standard deviations are shown for each series of analyses in the groups of rheumatoid arthritic and osteo-arthritic patients, together with the values for *t* and *P* (Fisher, 1941) which furnish statistical evidence of the significance of the differences between the means. It is evident from the values

for *P*, all of which exceed 0·05, that none of the pairs of mean values differ to a clearly significant extent. Hence, it is concluded that neither plasma creatine values nor levels of creatinuria are characteristically different in groups of patients who have the types of arthritis here studied.

If it is to be sought further, the possibility of finding a difference lies with greatest probability in the degrees of creatinuria shown by the groups of male patients (where values for *P* are least).

Many of the patients, both male and female, showed no creatinuria, and Table II presents a numerical distribution of cases based on the presence or absence of this finding, together with the ranges of principal values for creatinuria where this condition was found. Inspection of these ranges of values does indeed suggest that amongst male patients there exists a significant tendency for levels of creatinuria in rheumatoid arthritis (30 to 79 mg. per 12 hrs) to exceed those found in osteo-arthritis (11 to 24 mg. per 12 hrs). The numbers of male patients with creatinuria are too small for statistical enquiry to be helpful, but it is noteworthy as supporting evidence that the incidence of creatinuria in male arthritics was higher amongst the rheumatoid group (seven out of fourteen), than amongst the osteo-arthritic group (four out of fourteen).

TABLE II

NUMERICAL DISTRIBUTION OF 68 PATIENTS WITH VALUES FOR CREATINURIA

Creatinuria	Sex	Numbers of Patients and Ranges of Principal Values*		Total
		Rheumatoid Arthritis	Osteo-Arthritis	
Absent ..	F	8	9	17
	M	7	10	17
Present ..	F	11 6-22 mg. per 100 ml. 18-84 mg. per 12 hrs	12 2- 23 mg. per 100 ml. 12-126 mg. per 12 hrs	23
	M	7 3-17 mg. per 100 ml. 30-79 mg. per 12 hrs	4 2- 6 mg. per 100 ml. 11-24 mg. per 12 hrs	11
Total ..	..	33	35	68

* Values given in Table I, which exceeded the mean +2 S.D., are here omitted.

In order to apply statistical tests to the groups of all those with positive creatinuria, the results for male and female patients were combined (Table III, opposite). The mean values for the rheumatoids and osteo-arthritics do not differ significantly, the values for the statistic *P* being greatly in excess of 0·05.

It thus appears that a trend of difference in respect of creatinuria between patients with the two types of arthritis was demonstrable only in males. This finding is logical and to be expected, considering the small tendency for any such demonstrable difference to exist and the greater likelihood of its detection amongst males; for normal male adults excrete no creatine (or, infrequently, very little),

TABLE III
SUMMARY OF ANALYTICAL DATA FOR 34 PATIENTS IN WHOM CREATINURIA WAS FOUND

Creatine Estimation	Rheumatoid Arthritis (18: 11 female, 7 male)			Osteo-Arthritis (16: 12 female, 4 male)			Statistical Evaluation of the Difference between the Means	
	Range of Values*	Mean Value	S.D.	Range of Values*	Mean Value	S.D.	*t*	*P*
Urine creatine (mg. per 100 ml.)	3-27 (41)	15	9	2-27 (44)	13	11	0·58	0·6
Urine creatine (mg. per 12-hr night urine)	18-84 (144)	52	30	11-126 (158)	57	45	0·38	0·7

* A single value, where it exceeded the mean +2 S.D., is set out in brackets after the general range of values.

whereas normal females frequently exhibit degrees of creatinuria large enough to obscure any increment which may arise through the development of arthritis.

The method used for the determination of creatine also yielded values for creatinine concentrations. The plasma values were substantially normal throughout the whole series of patients, so that only the ranges (with mean values in italics) need be quoted (Table IV).

TABLE IV

Disease	Sex	Plasma (mg./100 ml.)
Rheumatoid Arthritis	Male	0·6—*1·0*—1·8
	Female	0·5—*0·9*—1·9
Osteo-Arthritis	Male	0·8—*1·0*—1·6
	Female	0·6—*0·9*—1·3

The output of urinary creatinine was correspondingly normal in every case.

Discussion

The results now presented indicate that no large or characteristic abnormality of creatine metabolism is likely to be found in chronic arthritis. The suggestion that there is a higher incidence and higher levels of creatinuria amongst males suffering from rheumatoid arthritis, compared with males who have osteo-arthritis, is in direct contrast to the conclusions put forward by Granirer (1949) concerning both male and female patients. Although it is now well established that creatinuria is common in many diseases affecting the general musculature, it seems unlikely that varying degrees of soft-tissue involvement complicating the cases of arthritis could account for the disparity of the opposite conclusions now being considered. Such variation amongst arthritic patients is, however, a probable factor influencing

the degree and frequency of creatinuria as it may be found amongst male patients with rheumatoid arthritis.

Reference has already been made to recent observations (quoted by Boland, 1950) on the influence of certain hormones on creatinuria in arthritic subjects. In the wider field, extensive studies of creatine metabolism in various endocrine disorders are still being pursued by many investigators, in the hope of clarifying our knowledge of the factors which influence the biochemistry of creatine. When these studies are more complete, the role of creatine in arthritic disorders will become more clearly defined.

Summary

(1) The views previously put forward by other workers concerning creatine metabolism in normal subjects and in patients with arthritis are briefly considered.

(2) The values for plasma creatine concentrations and the incidence and degree of creatinuria found in a series of forty females and 28 males are recorded. The analytical values have been examined statistically.

(3) No clearly significant differences could be detected between those with rheumatoid arthritis and those with osteo-arthritis, either males or females, in respect of plasma creatine concentrations or levels of creatinuria. Altogether seventeen males and seventeen females showed no creatinuria.

(4) No clearly significant differences in the degree of creatinuria, characteristic of the type of arthritis, could be found in those patients, eleven males and 23 females who were found to excrete creatine.

(5) Amongst the male patients a slightly higher incidence and a slightly greater degree of creatinuria did occur in the rheumatoid group than in the osteo-arthritic group. This trend was not demonstrable amongst the female patients. Possible explanations for these findings are suggested.

Our grateful appreciation is accorded to Miss P. Arnold for her practical assistance throughout this investigation.

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Métabolisme de la créatine au cours d'arthrite

RÉSUMÉ

(1) On considère brèvement les opinions des autres auteurs sur le métabolisme de la créatine chez les sujets normaux et arthritiques.

(2) Chez 40 femmes et 25 hommes on détermina le taux de la créatine dans le plasma et on nota sa fréquence et sa concentration dans l'urine. Les chiffres obtenus furent soumis à l'analyse statistique.

(3) On n'a pas pu déceler de différences nettement significatives entre les arthritiques rhumatisants et les ostéoarthritiques, hommes ou femmes, en ce qui concerne leur créatinémie ou créatinurie. Chez 17 hommes et 17 femmes il n'y eut pas d'excrétion urinaire de créatine.

(4) Chez les malades qui excrétaient de la créatine—11 hommes et 23 femmes—on ne trouva pas de chiffres suffisamment significatives pour caractériser le type d'arthrite.

(5) Les petites différences qu'il y avait concernaient la créatinurie qui, chez les hommes, était plus fréquente et plus accentuée dans les cas d'arthrite que dans ceux d'ostéoarthrite. Chez les femmes on ne vit pas de tendance semblable. On offre des explications de ces faits.

El metabolismo de la creatina en la artritis

SUMARIO

(1) Se considera brevemente las opiniones de otros autores sobre el metabolismo de la creatina en sujetos normales y artríticos.

(2) En 40 mujeres y 28 hombres se determinó los valores de la creatina en el plasma y se notó su frecuencia y su concentración en la orina. Los resultados fueron analizados estadísticamente.

(3) No fueron encontradas diferencias netamente significativas entre los casos de artritis reumatoide y los de osteoartritis, en hombres o en mujeres, respecto a creatinemia o creatinuria. No hubo creatinuria en 17 hombres ni en 17 mujeres.

(4) Los enfermos con creatinuria—11 hombres y 23 mujeres—no presentaron valores netamente significativos para poder caracterizar el tipo de artritis.

(5) Las pequeñas diferencias encontradas interesaban la creatinuria de los hombres; ésta era más frecuente y más acentuada en los casos de artritis reumatoide que en los de osteoartritis. En las mujeres no se vió tal tendencia. Se sugiere explicaciones de estos hechos.

SUBFASCIAL FAT HERNIATION AS A CAUSE OF LOW BACK PAIN

DIFFERENTIAL DIAGNOSIS AND INCIDENCE IN 302 CASES OF BACKACHE

BY

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(RECEIVED FOR PUBLICATION OCTOBER 22, 1951)

Subfascial fat herniation is a clinical entity in which fat herniates from a deep stratum to a more superficial one. It usually occurs in the lumbo-sacral or sacro-iliac region as a result of trauma, and is due to a weakened area of the deep layer of the superficial fascia. The chief characteristic is a single or multiple painful nodules which the patient is frequently able to localize. The pain is severe and the patient is actually unable to move when first seized by it. The symptoms and signs can be analogous to those that appear in a strangulated inguinal hernia. " Fibrositis " is the term frequently applied to this condition since the nodules were originally thought to be caused by excessive fibrous tissue. This is a report of 302 consecutive cases of previously undiagnosed low back pain.

Copeman and Ackerman (1944) first showed that these nodules were herniations of fat through the superficial fascia, and in other cases I have studied (Herz, 1946) their work was amply confirmed. When these nodules are located, either by the patient or by the examiner, an injection of 5 ml. 1 per cent. procaine underneath the nodules will produce startling and dramatic results, the patient being relieved of the pain within a few minutes; usually this relief is only temporary, but the injection serves as a diagnostic aid, and may be used repeatedly as a treatment.

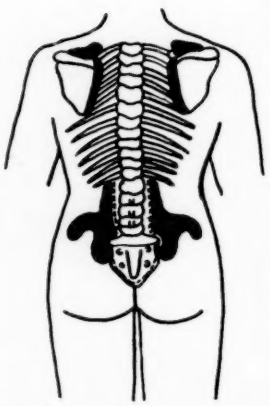

FIG. 1.—Distribution of fascial fat (Copeman and Ackerman, 1944).

Surgery is resorted to in those cases where the relief obtained from injection is too short or where repeated injections are impracticable.

Surgical removal of palpable nodules should never be attempted until after a thorough therapeutic test with injections of aqueous solutions of anaesthetic agents. If such injections do not relieve the pain there is little likelihood that an operation for subfascial fat hernia will give relief.

In the differential diagnosis a detailed history is very important, since a history of injury—such as a fall—is present in nearly all these cases. Often the onset of severe pain, as differentiated from an ache, is attributed

to a specific injury. It is important to find out the exact type of injury and its relationship to the pain of which the patient complains.

A careful physical examination with thorough palpation to elicit trigger points of pain and painful nodules is essential. Copeman and Ackerman (1944) found that the distribution of fat in the lumbar and lumbo-sacral area in an anatomical study of fourteen cadavers (Fig. 1) coincided almost exactly with the distribution of trigger points of pain in fifty consecutive cases (Fig. 2).

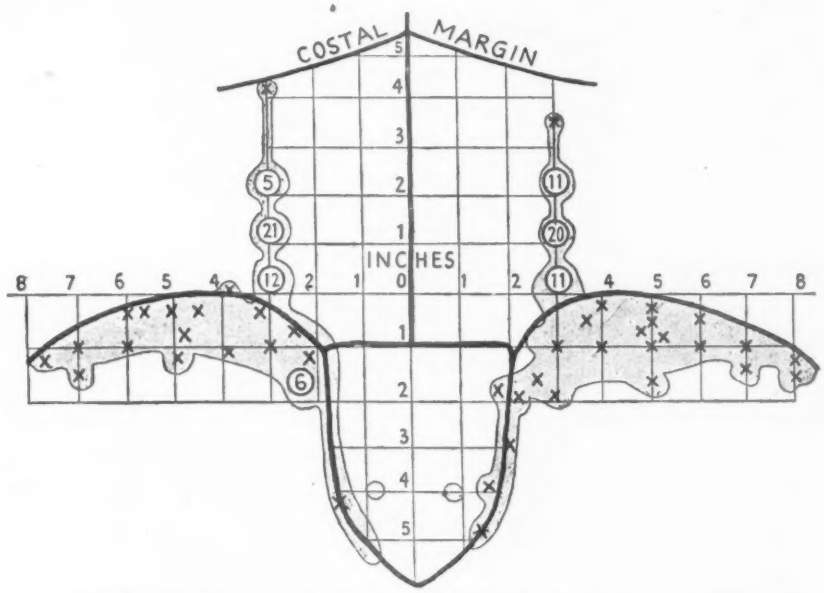

FIG. 2.—Distribution of trigger points of pain in fifty consecutive cases (Copeman and Ackerman, 1944).

Routine roentgenograms of the spine in antero-posterior, lateral, and oblique positions should be made to exclude disease or injury to the bone. The sacro-iliac joints should be clearly delineated, since involvement of these joints was often thought to be the cause of low back pain when actually the herniated fat was the causative agent.

It must also be remembered that more than one cause of low back pain may exist simultaneously. Painful nodules are frequently present when there is also evidence of arthritis of the spine. Treatment for arthritis alone will not relieve the patient, but the symptoms can be greatly relieved if injections of anaesthetic solutions are also given.

The possibility of an internal abdominal disease, such as retrocaecal appendicitis, nephrolithiasis, or gall-bladder disease, must naturally also be considered in the differential diagnosis of low back pain. Some of the many other causes of low back pain found were post-traumatic cysts pressing on the sciatic nerve (Herz, 1948), disrupted intervertebral disks, incomplete fracture of the lumbar spine, and spondylolisthesis (see Table, overleaf).

TABLE

CLINICAL DIAGNOSIS IN 302 CASES OF LOW BACK PAIN

Diagnosis	No. of Cases
Subfascial fat hernia relieved by operation	89
Painful nodules relieved by anaesthetic injections	92
Painful nodules with chronic arthritis of spine	39
Incomplete cases (relief followed one injection of anaesthetic solution to painful points, but no follow-up)	50
Undiagnosed (injection gave no relief and no other cause for backache was revealed)	8
Disrupted intervertebral disk (two also had subfascial fat hernias)	6
Post-traumatic cyst pressing on sciatic nerve	3
Tuberculosis of spine	1
Fractured coccyx	2
Incomplete fracture of lumbar spine	1
Spondylolisthesis (roentgenographic diagnosis)	3
Sacro-iliac dislocation (roentgenographic diagnosis)	3
Retrocaecal appendicitis	3
Renal calculus	2
Total	302

Technique of Operation for Fat Hernia Removal

The area of the herniated fat is marked with a dye before operation to compensate. It is blocked off with 30 to 50 ml. 1 per cent. novocaine. The skin is incised and the herniated fat is excised by sharp dissection (Fig. 3). The size of excised fat

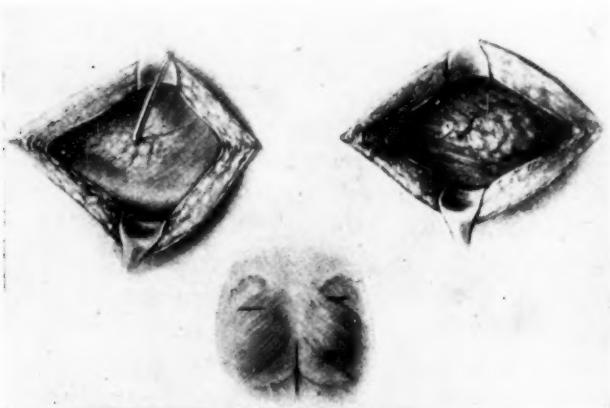

FIG. 3.—Incisions for subfascial fat herniotomy.

specimens is shown in Fig. 4, and a microscopic section of excised fat shows mild inflammatory process (probably traumatic) in Fig. 5. If the hernial opening cannot be located, the dissection is continued until the deep fascia is encountered. Haemostasis is then attended to and the wound sutured, preferably with stainless steel wire. A rubber dam drain is inserted and left *in situ* for one week to prevent

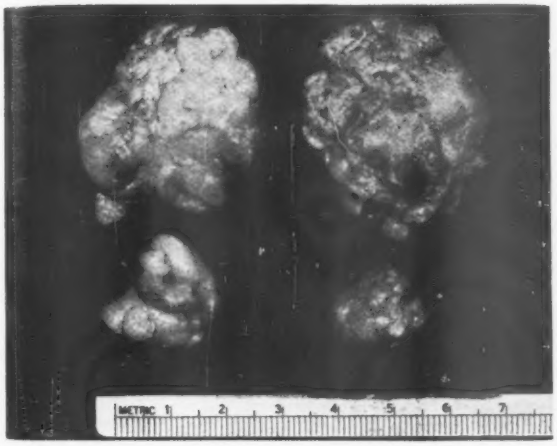

FIG. 4.—Excised fat specimens.

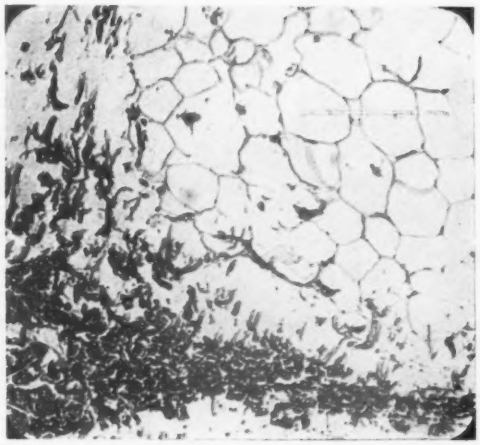

FIG. 5.—Microscopic section of excised fat, showing mild inflammatory process.

an accumulation of fluid in the wound and to facilitate healing. Dressings should be changed daily or more frequently depending on the amount of drainage. Sutures are removed in from 8 to 12 days. Wounds in the back do not heal as rapidly as those on the anterior part of the body.

Case Reports

Case 1, female, aged 34, had had recurrent attacks of lumbago for 17 years. Roentgenograms of the lumbar spine showed advanced osteo-arthritis. In addition, she had bilateral subfascial fat hernias which were treated surgically. The arthritis has not progressed materially since the operation 5 years ago, and the patient has had no further attacks of lumbago.

Case 2, female, aged 43, had a fall 2 years before she consulted me. Routine roentgenographic examination disclosed a fracture of the coccyx and injury to the sacrum. She had a subfascial fat hernia in addition. This was excised at the time of operation on the coccyx, and the patient obtained satisfactory relief.

Case 3, female, aged 46, suffered from severe backaches for 10 years after a fall, and had been treated for " arthritis " without obtaining relief. About a year before I saw her she had had a second severe fall which greatly aggravated her pain.

For several months she had extreme discomfort when sitting, and there was referred pain down the left leg. Since all therapeutic measures had failed, her physician concluded the pain was psychogenic. I found a trigger point of pain in the left sacro-iliac region and a large palpable mass in the left buttock. This was considered to be a case suitable for operation because complete relief was obtained by injections of 1½ per cent. aqueous metycaine solution. At operation, herniated fat was excised over the left sacro-iliac region, and a large mass of dense fibrous tissue was widely excised through an incision over the left buttock. Examination of the specimen showed an organized haematoma with multiple haemorrhagic cysts, which were pressing on the sciatic nerve. The patient had complete relief from her disability, and was able within a few months to make a 5,000-mile motor trip without any recurrence of symptoms.

Case 4, male, aged 37, had the first episode of pain in October, 1948, without known trauma. Pain extended from the right heel to the thigh. Symptoms persisted unabated despite various treatments until July, 1950. A subcutaneous fatty mass was located near the right sacro-iliac joint. A diagnostic test of injections with anaesthetic solutions gave

prompt relief of short duration, and operation was advised. The mass was excised and relief from pain was complete.

Case 5, female, aged 23, was involved in a motor accident in January, 1948, and suffered trauma to the back. She had had various treatments elsewhere, including 6 weeks in a plaster of Paris jacket, without relief. In July, 1949, several painful fatty nodules were injected, and the patient obtained the first relief from pain since the injury. Injections were repeated and operation was advised. This was performed in July, 1950. Relief was immediate and the patient recovered completely.

Summary

(1) The differential diagnosis and incidence of subfascial fat herniation as a cause of low back pain in 302 consecutive cases is discussed.

(2) Many of these cases had painful nodules in the back, and the pain was relieved by injections of anaesthetic solutions. In 92 cases, the symptoms were controlled by repeated injections at intervals, and operation was deemed unnecessary. Operation for removal of herniated fat was performed in 89 cases.

(3) In 39 cases which had these painful nodules in addition to chronic arthritis, varying degrees of relief from pain were obtained by anaesthetic injections.

(4) A complete history, thorough physical examination, and routine *x* rays are essential for the differential diagnosis. Some other causes of low back pain previously undiagnosed were post-traumatic cysts pressing on the sciatic nerve, disrupted intervertebral disk, arthritis, and retrocaecal appendicitis.

(5) The proportion of cases of subfascial fat hernias in this series is probably higher than normal because so many patients were referred to the author on account of his known interest in this condition. The large number in this series suggests, however, that many cases of undifferentiated low back pain rightly belong in this group, since a study of the literature indicates that relief has been obtained by the procedure described in many undiagnosed cases of low back pain.

Figs 1 and 2 are reproduced from Copeman and Ackerman (1944), by courtesy of the editors of the *Quarterly Journal of Medicine*, Clarendon Press, Oxford, and Messrs. E. and S. Livingstone, Edinburgh, publishers of " Text Book of the Rheumatic Diseases ", ed. W. S. C. Copeman.

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Hernie de la graisse sousaponévrotique comme cause de la douleur lombo-sacrée

Résumé

(1) On discute le diagnostic différentiel et l'incidence de la hernie de la graisse sousaponévrotique comme cause de douleur lombo-sacrée dans 302 cas consécutifs.

(2) Beaucoup de ces cas présentaient des nodules douloureux et la douleur fut apaisée par des injections des solutions anesthésiques. Dans 92 cas les symptômes furent enrayés par des injections répétées et une opération ne fut pas jugée nécessaire. L'extirpation chirurgicale de la graisse herniée fut effectuée dans 89 cas.

(3) Dans 39 cas qui avaient des nodules douloureux associés à l'arthrite chronique, on obtint un soulagement d'intensité variable à l'aide d'injections anesthésiques.

(4) Pour le diagnostic différentiel il est essentiel qu'on connaisse tous les antécédents, qu'on fasse un examen physique détaillé, et qu'on procède à des examens radiologiques réguliers. Parmi les nombreuses causes de la douleur lombo-sacrée, non reconnues auparavant, étaient des kystes post-traumatiques comprimant le nerf sciatique, un disque intervertebral luxé, une arthrite, et l'appendicite retrocécale.

(5) La proportion des cas de hernie de la graisse sousaponévrotique dans ce groupe est probablement au dessus de la normale du fait que de nombreux malades furent envoyés à l'auteur parce qu'on connaissait son intérêt à cette question. Le nombre élevé des cas suggère cependant que souvent la douleur lombo-sacrée non diagnostiquée appartient bien à cette catégorie; de plus, on trouve dans la littérature des cas qui furent soulagés par le procédé décrit, sans que le diagnostic ait été précisé.

Hernia del tejido adiposo subfascial como causa del dolor de la región lumbo-sacra

SUMARIO

(1) Se discute el diagnóstico diferencial y la incidencia de la hernia adiposa subfascial como causa del dolor en la región lumbo-sacra en 302 casos consecutivos.

(2) Muchos de estos casos tuvieron nódulos dolorosos y sintieron alivio después de inyecciones de soluciones anestésicas. En 92 cases los síntomas fueron controlados por inyecciones repetidas, y una operación no fué considerada necesaria. En 89 casos la grasa herniada fué extirpada quirurgicamente.

(3) En 39 casos de nódulos dolorosos conjuntamente con una artritis crónica fué conseguido alivio del dolor en grado variable por medio de inyecciones anestésicas.

(4) Una historia clínica completa, una exploración minuciosa, y un examen radiológico regular son esenciales para el diagnóstico diferencial. Entre otras causas numerosas de dolor lumbo-sacro, no reconocidas anteriormente, fueron: quiste post-traumático comprimiendo el nervio ciático, disco intervertebral dislocado, artritis y apendicitis retrocecal.

(5) La proporción de los casos de hernia adiposa subfascial en este grupo es probablemente elevada, debido a que muchos enfermos fueron referidos al autor por conocerse su interés en esta cuestión. El gran número de estos casos sugiere, sin embargo, que muchas veces el dolor lumbo-sacro no diferenciado pertenece a la categoría estudiada; se encuentran además en la literatura casos de dolor semejante, aliviados por el procedimiento descrito, sin que el diagnóstico hubiese sido precisado.

RHEUMATOID ARTHRITIS OF MENOPAUSAL WOMEN TREATED WITH INSULIN HYPOGLYCAEMIAS

BY

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A favourable response to insulin hypoglycaemias (I.H.) or adrenaline infusions, in one case of rheumatoid arthritis and in two cases of non-articular rheumatism, has already been described (Godlowski, 1949). Since then Kersley and others (1950) have found in a series of forty cases of various aetiological types of rheumatoid arthritis treated with I.H., a significant improvement in 31, no response at all in eight, and a definite deterioration while under treatment in one. In their further observations (Kersley and others, 1951), they showed that the 44 per cent. of cases showing initial marked improvement diminished to 10 per cent. in the course of a 6-months' follow-up. Greif and others (1950) found clinical remission in three out of four cases of rheumatoid arthritis with I.H., but in the fourth a clinical deterioration took place during treatment.

The present series of ten cases deals only with rheumatoid arthritis in menopausal or post-menopausal women.

Method

Material.—All ten patients were women whose menopause began from one to 20 years ago. The duration of the symptomatology of rheumatoid arthritis varied from a few months to 18 years, the onset of the articular pathology having been more or less closely related to the beginning of menopausal symptoms. In none was there any history of rheumatic fever or episodes of rheumatoid arthritis before the onset of the menopause.

Routine Investigations.—For two control weeks of hospitalization each patient was kept in bed without any treatment, and the following investigations were carried out:

Weekly: measurement of bodyweight, erythrocyte sedimentation rate (Westergren), circulating eosinophil count (Randolph, 1944);
haemoglobin and erythrocyte count;
leucocytosis.

24-hourly: measurement of urinary output of 17-ketosteroids and 11-oxycorticoids (Tompsett and Oastler, 1946, 1947);
urinary output of creatinine (Folin, 1914), and of uric acid (Benedict and Franke, 1922).

In the next 2 to 4 weeks, during the actual treatment, this series was repeated twice.

In the last 2 weeks of withdrawal each patient again remained without any treatment, and the same series of investigations was repeated at the end of the period.

Insulin Hypoglycaemia.—This was produced by a subcutaneous injection of soluble insulin at 8 a.m. to a fasting patient. The dosage of insulin fluctuated between 20 and 80 units, and caused well-developed clinical symptoms of hypoglycaemia (Godlowski, 1946). The discontinuation of I.H. was carried out by giving the patient a tumbler of highly-sugared water followed by a meal rich in carbohydrates. The I.H. was applied daily for a period of from 14 to 28 days.

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Results

The most constant and significant improvements obtained by insulin hypoglycaemia therapy in this series were as follows:

(*i*) definite increase in bodyweight in nine out of ten cases.
(*ii*) diminution of pain, stiffness, oedema, and atrophy in nine out of ten cases.
(*iii*) striking improvement in muscular strength in the hands in six out of the nine positive cases.

During and immediately after treatment the erythrocyte sedimentation rate fell significantly in eight out of ten cases, although only in three did it return to normal levels (all these three had a relapse within 2 months of discontinuing the treatment). Of the eight cases which showed initial improvement in the erythrocyte sedimentation rate estimations, three showed a significant increase by the end of the withdrawal period. The haemoglobin and red blood count, if materially subnormal, either returned to normal levels or showed a tendency towards it (no iron therapy was given). The circulating eosinophils in all nine positive cases were significantly diminished during the period of I.H. treatment and returned to their initial level in the withdrawal period. The 24-hr excretion of steroids and nitrogen in the urine showed no significant change.

All the cases relapsed, three with significant deterioration of the whole clinical picture, in the course of a ten-months' follow-up period.

Although the one negative case made some progress during the period of I.H. treatment (mainly in bodyweight and muscular strength), the rest of the signs and symptoms persisted in their initial intensity at the end of the treatment and further deterioration was noticed in the follow-up period; thus this case is regarded as not responding to the treatment at all, and such insignificant improvement as did occur may be ascribed merely to hospitalization.

Discussion

Ten cases of rheumatoid arthritis in menopausal or post-menopausal women were treated daily with I.H. for a period of 2 to 4 weeks, with a significant improvement in nine cases. In the 2 weeks of the withdrawal period this improvement still persisted, and in some cases further improvement occurred. The erythrocyte sedimentation rate in all nine positive cases was reduced, but returned to normal levels in only three. The slowing down of the erythrocyte sedimentation rate may be interpreted as showing that the cause of its acceleration was only partially and temporarily affected by I.H.; in other words, if increased erythrocyte sedimentation rate signifies the activity of the morbid process, so I.H. only partially and temporarily affected the primary aetiological factor of rheumatoid arthritis of menopausal type.

In view of the early relapsing of the full symptomatology of all nine positive cases, and in view of the persistence of a high, though slightly reduced, erythrocyte sedimentation rate, the positive results obtained by I.H. should be regarded as a conditional elimination of the aetiological factor and not as a permanent modification of the primary agent operating in the morbid process. The lack of

permanent improvement with I.H. therapy in the menopausal type of rheumatoid arthritis should not be taken to apply to all the aetiological types of the disease, because this represents a separate entity in which the primary pathogenic factor initiating the articular pathology has probably an individual mode of action.

Further investigations of the mechanism of the beneficial action of I.H. in the conditional alleviation of menopausal and other types of rheumatoid arthritis, and in various anaphylactic conditions, are in progress.

Summary

(1) Nine out of ten cases of rheumatoid arthritis in menopausal or post-menopausal women treated with insulin hypoglycaemias responded with clinical remission; one case showed no significant clinical change.

(2) Nine cases relapsed in the course of the next 10 months, and in some the articular pathology progressed more rapidly than in the pre-treatment period.

(3) The results obtained by insulin hypoglycaemia in the treatment of this type of rheumatoid arthritis should be regarded as a temporary slowing down of the pathological processes.

(4) Since all the treated cases relapsed, this form of treatment should be regarded as having only a conditional and temporary effect.

We wish to thank J. Fitzpatrick, B.Sc., A.R.I.C., biochemist to the Ayr County Laboratory, Central Hospital, Irvine, for the estimations of the urinary steroids, uric acid, creatinine, etc.

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Arthrite rhumatismale au cours de la ménopause traitée par l'hypoglycémie insulinique

RÉSUMÉ

(1) Neuf cas sur dix d'arthrite rhumatismale durant ou après la ménopause traités par l'hypoglycémie insulinique, accusèrent une amélioration clinique; dans le dixième cas il n'eut pas de modification clinique significative.

(2) Neuf cas ont eu une rechute avant que dix mois se soient écoulé, et pour certains d'eux la pathologie articulaire s'avança plus rapidement qu'avant le traitement.

(3) Les résultats obtenus dans le traitement de ce type d'arthrite rhumatismale doivent être considérés comme un ralentissement temporaire des processus pathologiques.

(4) Tous les malades traités ayant eu des rechutes, cette forme du traitement doit être considérée incapable de produire un effet autre que conditionnel et temporaire.

Artritis reumatoide de menopáusicas tratada con hipoglicemia insulínica

SUMARIO

(1) De diez casos de artritis reumatoide menopáusica o postmenopáusica tratados con hipoglicemia insulínica, nueve respondieron con mejoría clínica y el décimo quedó sin cambio clínico significante.

(2) Los nueve casos tuvieron una recaída en el curso de los diez meses que siguieron el tratamiento y en algunos de ellos la patología articular progresó más rapidamente que antes del tratamiento.

(3) Los resultados obtenidos en el tratamiento con hipoglicemia insulínica de este tipo de artritis reumatoide deben estimarse como retardación pasajera de los procesos morbosos.

(4) A la vista de tantas recaídas, esta forma de tratamiento debe considerarse capaz de producir tan sólo efectos condicionales y pasajeros.

FAMILIAL INCIDENCE OF RHEUMATOID ARTHRITIS AND ACUTE RHEUMATISM IN 100 RHEUMATOID ARTHRITICS

BY

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It is comparatively rare in clinical medicine to encounter a condition which can be shown to be inherited as a simple Mendelian gene. As Crew (1947) pointed out, the human subject is by no means satisfactory to study from a genetic point of view; his mate is not chosen for him, he matures slowly, he has few offspring, his chromosomes are numerous, and his mutation rate cannot be speeded up with *x* rays.

The best we can hope to do, in most diseases, is to show whether or not an heredito-familial tendency is involved. The final picture is modified partly by the powers of penetration of a gene or the modifying influence of other genes, but chiefly by the incalculable effect of environment factors. In those conditions where such a tendency can be shown to exist it is important to establish it and, conversely, to disprove it where absent. This will assist us in our understanding of the aetiology, diagnosis, and prognosis.

Our knowledge of the aetiology of rheumatoid arthritis remains imperfect. The report by the Scientific Advisory Committee of the Empire Rheumatism Council (1950) is probably the most exhaustive clinical investigation on this subject ever undertaken in Great Britain. The results were reached after careful analysis of the case histories of 532 patients and 532 controls. Investigations into a large number of factors commonly believed to influence the onset of rheumatoid arthritis produced largely negative results.

However, in the case of familial factors, the results obtained lend support to the view that these are of aetiological significance. 7 per cent. of the fathers of patients as opposed to 3 per cent. of the fathers of controls suffered from arthritis; 15 per cent. of the mothers of patients as opposed to 9 per cent. of the mothers of controls suffered from arthritis; of 2,151 brothers and sisters of patients, 82 (3·8 per cent.) had arthritis, and of 2,143 brothers and sisters of controls, 38 (1·8 per cent.) had arthritis. These figures are considered to be statistically significant. However, the report adds:

> The relatively low incidence of a family history of arthritis and the greater likelihood of the patients remembering relatives afflicted with the disease as compared with the controls necessitates withholding any final conclusions on the matter until further investigations have been undertaken.

Present Investigation

I considered that it would be worth while to study the family histories of a series of rheumatoid arthritics in relation to rheumatoid arthritis and acute rheumatism. If a family history of arthritis is recorded, cases of osteo-arthritis and gout are presumably included. The former is generally attributed to a degenerative process either secondary to trauma, skeletal abnormality, or infection, or due to senile changes, though it may be argued that an inherited weakness of joint structure is present. The relationship of gouty arthritis to rheumatoid remains obscure. On the other hand, rheumatoid arthritis is an active disease process, with a tendency to exacerbations and remissions which are often spontaneous. (Hench, 1949, estimated that striking remissions are only obtained in 15 per cent. of cases as a result of treatment—rest, physical therapy, gold, etc.—but occur in 60-90 per cent. of cases during jaundice or pregnancy.) Clinical observation suggests that this disease bears a close relationship to acute rheumatism. This may be inferred by the close similarity between the histology of the nodules in the two conditions. Dawson (1933), comparing subcutaneous nodules in rheumatic fever and rheumatoid arthritis, considers that:

> These studies . . . lend further support to the conception that rheumatic fever and rheumatoid arthritis are intimately related and possibly different responses of affected individuals to the same aetiological agent.

Furthermore, a considerable number of cases develop acute rheumatism, which is followed directly, or after a latent period, by the development of polyarthritis indistinguishable from rheumatoid arthritis. Other cases are seen with evidence of rheumatic carditis and rheumatoid arthritis in which a history of acute rheumatism may or may not be given (8 per cent. of the cases in this series were recorded as having suffered from acute rheumatism, or as having definite evidence of rheumatic heart disease). Finally, both conditions are known to respond to cortisone and ACTH, and I hope to show that there exists in certain families a tendency to develop either rheumatoid arthritis or acute rheumatism.

Rheumatoid and osteo-arthritis are clearly divided into two broad groups in the classification of arthritis suggested by a Scientific Committee of the Royal College of Physicians (1934). Acute rheumatism is put into a separate category in this classification.

Material

Patients Examined.—One hundred unequivocal cases of rheumatoid arthritis have been studied. All cases exhibited the typical symmetrical joint involvement affecting chiefly the small peripheral joints. Routine investigations included *x* rays of the most affected joints, estimations of the blood sedimentation rate, blood uric acid, and Wassermann reaction, and any other special investigations which were indicated. There was otherwise no selection of cases. 81 per cent. of the cases studied were females, and 19 per cent. males. The proportion of females is higher than in most series, and is probably accounted for by the fact that women tend to come to clinics more regularly than men, especially

when the latter have to take time off from work. Thus, when cases are recorded as they attend the clinics, a rather higher proportion of female patients is recorded than is justified by the true sex distribution. The mean age of the patients, when first seen, was 43 for males and 49 for females. The difficulty in fixing any exact date of onset in many cases makes an accurate estimate of the mean age of onset impossible.

In any investigation of this kind a certain number of cases in the families of cases and controls are inevitably missed, either through the persons being unaware of the existence of affected members in their families, or through doubt as to the exact nature of the disease. Although the Report of the Empire Rheumatism Council mentions the possibility that patients may be more likely to remember afflicted members of their families, it does not seem probable that the error from this cause is significant. Arthritis of any severity is such a striking disease that controls will probably be quite as likely as patients to know of its occurrence in their families. Acute rheumatism is not generally connected with arthritis by the lay public, and rheumatoid arthritics are unlikely to have any special knowledge of its occurrence in their families. In the few cases recorded in grandparents very special care was taken to ensure that only true rheumatoid cases were included. Naturally many cases must have been missed, and many cases of arthritis in grandparents were mentioned in which no exact diagnosis could be made. In 33 cases occurring in families of patients and controls the diagnosis of acute rheumatism (as shown by the presence of rheumatic heart disease) or rheumatoid arthritis was checked by personal observation, either in the home or clinic. In a further 21 cases the diagnosis was confirmed by a medical practitioner with knowledge of the case. In the remaining 52 cases no such check was possible, and the patient's history (or in some cases the history of a parent) had to suffice. The question " What type of arthritis ? " was asked. Only when the patient was able to state that it was rheumatoid arthritis, and subsequent questioning made this diagnosis seem highly probable, was the case included. In the case of acute rheumatism little ambiguity is possible.

Controls.—One hundred control cases were selected, chiefly from patients admitted for treatment for traumatic conditions and for abdominal surgery. Any person who gave a history of " rheumatism ", or arthritis of any sort, was excluded. For each patient, a control was selected of the same sex, and within 5 years of the same age.

Some of the family histories of controls were not without interest. One lady, aged 37, had nursed her paternal grandfather and her paternal grandmother who were both sufferers from rheumatoid arthritis. In spite of this family history from both sides, only one of her father's four sisters had developed rheumatoid arthritis, and no other member of the family had suffered from arthritis or acute rheumatism. Another lady, aged 35, gave a history of rheumatoid arthritis affecting her maternal grandmother; her mother's generation had escaped, but she had two brothers and two sisters affected with the disease, though she had escaped herself.

One control gave a history of rheumatoid arthritis in her mother and in one sister; another a history of rheumatoid arthritis in her grandmother and of rheumatic fever in her brother, and another of rheumatic fever in one brother and one sister. The other eighteen cases of rheumatoid arthritis or acute rheumatism recorded in the family histories of controls were scattered singly over the whole group.

One lady, aged 48, gave an entirely negative personal history. Her father, however, had had rheumatic fever and had died of rheumatic heart disease, and one brother had suffered from rheumatic fever. On closer questioning she admitted to a short attack of chorea as a girl, and an examination revealed a mitral lesion in the heart, which had previously not been suspected. She was accordingly excluded from the control group, but the case serves to show that help may be obtained from the family history when rheumatic carditis is suspected.

Analysis of Cases and Comparison with Controls

Table I gives the incidence of acute rheumatism and rheumatoid arthritis in the families of cases and controls.

TABLE I
INCIDENCE OF RHEUMATIC DISEASE

Family Relationship	Cases			Controls		
	Total	No. Affected	%	Total	No. Affected	%
Grandparents	400	6	1·5	400	4	1
Fathers	100	5	5	100	2	2
Mothers	100	13	13	100	8	8
Uncles and Aunts ..	470	9	1·9	454	3	0·66
Brothers	164	14	8·5	173	5	2·9
Sisters	174	27	15·5	170	10	5·9
Total	1,408	74	5·3	1,397	32	2·3

A higher proportion of cases is recorded among parents, brothers, and sisters, than among more distant relatives. This is probably due to greater accuracy in the histories relating to close relations, and to the fact that a domiciliary visit may provide confirmation of a doubtful history in this group, whereas grandparents, uncles, and aunts are less readily available.

The incidence in females is greater than in males, as we should expect, and in all groups the incidence is greater in the families of patients than in those of controls. If we confine ourselves to the study of parents, brothers, and sisters only, a much higher proportion of cases is recorded and the discrepancy between patients and controls is more marked.

Of 538 members of the families of patients there were 59 (11 per cent.) affected members.

Of 543 members of the families of controls there were 35 (4·6 per cent.) affected members.

Cases of acute rheumatism or rheumatoid arthritis in nephews, nieces, and sons, or daughters were of course quite often mentioned by patients, but little accuracy is possible when dealing with more distant relatives. Furthermore, a study of the younger age groups does not assist us materially. Occasional cases of acute rheumatism will be found, but not many will have had time to develop rheumatoid arthritis.

The familial incidence of rheumatoid arthritis and acute rheumatism is again demonstrated by a study of the distribution of cases among the families of patients and controls (excluding controls with negative family histories, i.e. 77 control families). Thus we have 123 families; 100 families of cases and 23 families of controls, with affected members. Among these 123 families there were 206 affected members, 106 among the families of patients and controls, and the original 100 cases. Table II gives the distribution of affected members:

TABLE II

DISTRIBUTION OF AFFECTED MEMBERS OF FAMILIES

No. of Cases in Family	No. of Families	Total No. of Cases		
7 5 4 3	1 1 4 13	7 5 16 39	67	32·5%
2	35		70	34%
1	69		69	33·5%

On these figures, we may conclude that we may expect a family history of rheumatoid arthritis or acute rheumatism affecting more than two members of the family in one-third of rheumatoid arthritis patients, in one-third there will be one other affected member, and in one-third the family history will be negative.

As the proportion of affected members is higher in the families of patients in every group studied, arithmetical tests of significance were not considered to be of great importance.

It is not suggested that final conclusions have been reached, but it is hoped that the above figures may help to establish as a scientific fact that in certain families there exists an heredito-familial tendency towards the development of acute rheumatism or rheumatoid arthritis, and further investigations would be of great interest.

Discussion

Selye (1950), with his conception of a "General Adaptation Syndrome", attempts to show that a variety of diseases, including rheumatoid arthritis, arise as a result of the body's failure to adapt itself to various stresses. Agents producing stress can act specifically, producing specific injuries, and non-specifically, producing the "Alarm Reaction" (i.e. tissue catabolism, hypoglycaemia, gastro-intestinal erosions, discharge of secretory granules from the adrenal cortex, and haemo-concentration). During the stage of resistance these manifestations disappear or are actually reversed. Should the body become incapable of further resistance a state of exhaustion is reached and these manifestations may reappear. The failure of the body to adapt itself to non-specific local or systemic injuries may result in the appearance of various stress diseases, and exactly which disease appears in a given individual is due to conditioning factors such as heredity, diet, or previous exposure to stress.

Selye's theory assumes that an individual's power of adaptation is a finite quantity greatly dependent upon genetic factors, and our present clinical observations on the heredito-familial tendency to "rheumatic" diseases in certain families accords well with this theory. We may assume, if we accept Selye's theory, that individuals in such families succumb to rheumatoid arthritis and acute

rheumatism after exposure to " stressors " (i.e. agents producing both stress and specific actions) more easily than normal individuals through an hereditary weakness in their adaptation mechanism.

Kendall, in his Heberden Oration (1951), points out that rheumatoid arthritis " is not an endocrine disease in the usual sense of the term ". Patients with Addison's disease are not particularly liable to develop rheumatoid arthritis, and there is no evidence that cortisone is not produced in normal amounts in rheumatoid arthritics.

After discussing other possible causes, such as imbalanced production of cortisone and the amorphous fraction, or the production of a rheumatogenic agent by the adrenal cortex, Kendall tends to the view that a hypersensitivity state may underlie rheumatoid arthritis. (He later points out that rheumatoid arthritis and rheumatic fever " are not far separated in their nature and in their response to cortisone "). If the diseases are, in fact, hypersensitivity reactions to a foreign protein, cortisone might act either by modifying its rate of production, or by protecting the tissues from the effect of the products of this antigen-antibody reaction, as it has been shown to do in many other conditions.

I should like to carry this line of thought a step further. We know that in certain families there exists a marked constitutional tendency towards the development of certain hypersensitivity states; asthma, hay fever, and urticaria are common examples, though of course many cases of these maladies are seen in which there is no relevant family history. In these families the effects of the products of an antigen-antibody reaction are most marked in certain tissues, the bronchial or nasal mucosa, or the skin and subcutaneous tissues, as the case may be.

May it not be that in certain families there is a constitutional tendency to react through the medium of the synovial membranes ? We might then explain the action of cortisone as modifying the effect of such a reaction. In this connection it is perhaps interesting to note that the antihistamine drugs have not proved effective in treating asthma, whereas cortisone produces a dramatic effect in most cases.

Meanwhile, from the practical point of view, a careful family history should always be taken in cases of suspected rheumatoid arthritis, especially in patients in the pre-arthritic stage when diagnosis is difficult. When several members of the family have suffered from rheumatoid arthritis or acute rheumatism, the onset of such prodromal symptoms as joint or muscle pains, migrant joint swellings, or paraesthesiae, in an individual are particularly likely to indicate the onset of rheumatoid arthritis. Such a family history may also be helpful in establishing the diagnosis in cases of suspected rheumatic carditis and valvular disease of the heart.

Summary

The familial incidence of rheumatoid arthritis and acute rheumatism was compared in 100 rheumatoid arthritics and 100 controls.

The incidence of these diseases was found to be more than twice as frequent

in the families of patients as in those of the control group: 5·3 per cent. and 2·3 per cent. respectively, when grandparents, parents, uncles, aunts, brothers, and sisters were included; 11 per cent. and 4·6 per cent. respectively, when only parents, brothers, and sisters were included.

From the figures obtained in this series, it is concluded that approximately one-third of rheumatoid arthritics will give a family history of rheumatoid arthritis or acute rheumatism in two or more members of their families (as many as seven affected members were recorded in one family of sixteen); approximately one-third will give a history of one affected member; the remaining one-third will give a negative family history.

It is suggested that an heredito-familial tendency towards the development of acute rheumatism or rheumatoid arthritis occurs in certain families.

The occurrence of such a constitutional tendency is discussed in relation to Selye's "General Adaptation Syndrome" and Kendall's view that a hypersensitivity state may underlie rheumatoid arthritis: as regards the former, certain individuals may have an hereditary weakness in their adaptation mechanism; as regards the latter, it is suggested that certain individuals may have a constitutional tendency to react to the effects of the products of an antigen-antibody reaction through the medium of the synovial membranes.

The cases in this series were under the care of Dr. J. Shulman, Physician-in-Charge, Department of Physical Medicine, Coventry and Warwickshire Hospital, and I am most grateful for his permission to publish them.

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La fréquence de l'arthrite rhumatismale et du rhumatisme articulaire aigu dans les familles des 100 arthritiques rhumatisants

RÉSUMÉ

La fréquence familiale de l'arthrite rhumatismale et du rhumatisme articulaire aigu chez 100 arthritiques rhumatisants fut comparée à celle chez 100 témoins.

On trouva que les affections rhumatismales étaient deux fois plus fréquentes dans les familles des malades que dans celles des témoins: 5,3 et 2,3 pour cent respectivement, quand il s'agissait de grands-parents, parents, oncles, tantes, frères, et soeurs; 11 et 4,6 pour cent respectivement, quand on ne considéra que les parents, les frères, et les soeurs.

D'après les chiffres obtenus, on peut conclure qu'un tiers environ d'arthritiques rhumatisants présente des antécédents familiaux d'arthrite rhumatismale ou de rhumatisme articulaire aigu frappant deux parents ou plus (dans une famille de seize on trouva sept affectés); dans un autre tiers environ un membre se trouve affecté, et le dernier tiers n'a pas d'antécédents familiaux.

On suggère que certaines familles ont une tendance hérédo-familiale à contracter le rhumatisme articulaire aigu ou l'arthrite rhumatismale.

On discute l'existence d'une telle tendance à la lumière du " syndrome d'adaptation générale " de Selye et de l'opinion de Kendall qu'un état d'hypersensibilité forme la base de l'arthrite rhumatismale: si on acceptait la théorie de Selye, le mécanisme d'adaptation de certaines personnes souffrirait d'une faiblesse héréditaire, et si on suivait celle de Kendall, il faudrait admettre l'existence chez certains sujets d'une tendance constitutionnelle à réagir contre les produits de la réaction entre l'antigène et l'anticorps par l'intermédiaire des membranes synoviales.

La incidencia familiar de la artritis reumatoide y del reumatismo articular agudo en 100 artríticos reumatoides

SUMARIO

Se comparó la incidencia de la artritis reumatoide y del reumatismo articular agudo en las famillas de 100 artríticos reumatoides y en las de 100 testigos.

Resultó que las afecciones reumáticas ocurrían con una frecuencia más de dos veces mayor en las famillas de los enfermos que en las de los testigos: 5,3 y 2,3% respectivamente al tratarse de abuelos, padres, tíos y hermanos de ambos sexos; 11 y 4,6% respectivamente, tomando en cuenta sólo á los padres y hermanos de ambos sexos.

Según las cifras obtenidas, se puede concluir que cerca de una tercera parte de los casos de artritis reumatoide o de reumatismo articular agudo tendrán antecedentes familiares de artritis reumatoide o de reumatismo articular agudo afectando dos o más parientes (en una familia de 16 personas hubo siete afectados !); en otra tercera parte aproximadamente habra un miembro afectado y en la restante tercera no habrá antecedentes familiares.

Se sugiere que ciertas familias tienen una tendencia heredo-familiar a contraer la artritis reumatoide o el reumatismo articular agudo.

Se discute la existencia de tal tendencia en relación con el " síndrome de adaptación general " de Selye y con la opinión de Kendall, según la cual un estado de hipersensibilidad formaría la base de la artritis reumatoide: si se aceptara la teoría de Selye, el mecanismo de adaptación de ciertas personas sufriría de una debilidad hereditaria; al seguir la de Kendall, habría que admitir la existencia en ciertos sujetos de una tendencia constitucional a reaccionar contra los productos del encuentro entre el antigeno y el anticuerpo por medio de las membranas sinoviales.

OBSERVATIONS ON THE USE OF THIOURACIL IN RHEUMATOID ARTHRITIS

BY

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No reports have been published on the possible effects upon rheumatoid arthritis of the thiouracil drugs, which have a potent action on the thyroid and also on the adrenal glands, although several investigators have pointed out certain correlations between disturbances of the thyroid on the one hand, and rheumatoid arthritis on the other, and the study of the adrenal cortex plays a central role in rheumatology. Tripi and others (1949) certainly observed in a careful investigation that rats treated with thiouracil developed a more severe experimental arthritis than control animals. However, these animal experiments are not directly applicable to human rheumatoid arthritis, particularly as the animals suffered from a septic arthritis quite different from the human disease. The rats were inoculated with a "pleuropneumonia-like organism"; in connection with the developing joint affections, abscesses were to be found in several organs, and the inoculated micro-organisms could be cultivated both from various organs and from the joints in pure culture.

The experimentation with thiouracil medication in cases of rheumatoid arthritis was initiated by a case in which thiouracil seemed to have a favourable action.

In 1947, a woman of 65 was admitted to our clinic, after having suffered for 7 years from rheumatoid arthritis and thyrotoxicosis which had appeared at about the same time and had progressed year by year. As the patient would not submit to an operation, which was recommended because of the severe symptoms of thyrotoxicosis, treatment with thiouracil was started in the ward. During this treatment, the symptoms of both thyrotoxicosis and rheumatoid arthritis disappeared simultaneously in the course of a month. The active swelling of the joints regressed, the articular pain disappeared, and the mobility of the joints recovered almost to normal. The erythrocyte sedimentation rate fell from 25 to 11 mm., and the Hb value rose from 79 to 86 per cent. About six months after leaving the hospital the patient stopped the use of thiouracil; within less than a month the articular symptoms began to show signs of aggravation, but they recovered their previous condition when medication was resumed. After about a year, the patient again stopped the use of thiouracil; within 2 months the joint affections began to show an exacerbation, and, at the same time, the symptoms of thyrotoxicosis appeared in a more severe form than before. Medication with thiouracil, which was again given in the hospital, again had a favourable action on both diseases.

Since a recovery from the symptoms of rheumatoid arthritis was observed

repeatedly in this present case during thiouracil medication, this drug has been tested on some other cases of rheumatoid arthritis.

Material

The material consists of ten cases of rheumatoid arthritis. One of these patients was suffering at the same time from manifest thyrotoxicosis, and two of the others exhibited slight symptoms suggestive of the latter disease. The remaining seven showed no signs of disturbance in thyroid function.

The patients were given methyl- or propyl-thiouracil, the amount varying between 7·8 and 51·6 g. The duration of the treatment varied from 17 to 86 days. All the medication was carried out while the patients were in hospital.

The distribution of the material and the main results are shown in the Table (opposite).

As seen in the Table, distinct clinical improvement was observed during the treatment in eight out of the ten cases. (In one case, in which the thiouracil treatment was repeated after approximately two years, even this second course of medication was followed by a rapid recovery of the articular symptoms.) Five of the patients showed a rapid and marked improvement during the thiouracil treatment. In the three other cases, distinct improvement was also observed, but the recovery did not differ from those results which can be obtained in favourable cases with the aid of hospital treatment in general (excluding, of course, the rapid temporary disappearance of symptoms on administration of cortisone or ACTH). The clinical picture of two of the patients did not show any marked objective changes. Subjectively, the patients reported a slight reduction in pain. No aggravation of the symptoms was observed in any of the patients.

In analysing the improvement observed during the thiouracil medication, it has to be taken into account, of course, that these patients also received the usual general hospital treatment (rest in favourable hospital conditions, suitable nutrition, vitamins, etc.), and physical treatment and the usual anti-rheumatic drugs (salicylates against pain, etc.) were used. It must also be remembered that rheumatoid arthritis is a disease with a spontaneously fluctuating course. This makes an assessment of the efficacy of therapeutic measures difficult (for instance, opinions on the value of the gold treatment, which has been in use for years, are still at variance). However, after paying due attention to these factors, the improvement observed during the course of the thiouracil medication in the rather active symptoms of rheumatoid arthritis in the above five cases was still unusually pronounced. In four of these cases, the results must be given the greater significance as the patients had been suffering from their disease for 3-13 years, and several other methods of treatment had been tried, with rather meagre results. The fifth case was one of a patient in whom a rheumatic relapse had appeared in active form about a month before, and thus, the rapid recovery was not so spectacular as that seen in the other cases.

Discussion

Since the present results suggest that thiouracil may have a favourable action on the course of rheumatoid arthritis, the problem arises: what is the mechanism of this effect ?

The best known effect of thiouracil, the reduction of the secretion of the thyroid (thiouracil is understood to inhibit the synthesis of thyroxin), can hardly play a marked role in rheumatoid arthritis. True, there are reports on a recovery from rheumatoid arthritis in connection with the operative or *x*-ray treatment of thyrotoxicosis from which the patient had been also suffering (Bauer and Camp, 1935; Curschmann, 1925; Deusch, 1922; Duncan, 1932; Viersma, 1936).

TABLE

CHANGES IN SYMPTOMS OF RHEUMATOID ARTHRITIS (RA) DURING ADMINISTRATION OF THIOURACIL

Case No.		1	2	3	4	5	6	7	8	9	10a	10b
Age and Sex		26 M	27 F	28 F	29 M	36 M	43 M	44 M	47 F	55 M	65 F	68 F
Duration of RA (in years if not otherwise stated)		1½	1½	1	9	5	1 mth (relapse)	1½	2	13	7	10
Thiouracil preparation used M = Methyl thiouracil P = Propyl thiouracil		P	M	M	M	M	M	M	P	P	M	P
Total amount of Thiouracil (g.)		11·8	11·6	8·0	8·6	13·8	10·0	51·6	7·8	10·0	12·6	14·6
Days during which Thiouracil was administered		57	74	24	17	23	25	86	36	50	30	81
Joint Symptoms	Active Swelling (Before)	+	++	++	+?	++	++	++	+	+	++	++
	Active Swelling (After)	+	+	0	0	0	0	+?	+	0	0	0
	Restriction of Mobility (Before)	++	++	++	+	++	++	++	+	++	++	++
	Restriction of Mobility (After)	++	+	0	+	+	0	+	+	+	+?	+?
	Articular Pain (Before)	++	++	++	+	++	++	+ +	+	++	++	++
	Articular Pain (After)	++	+	0	0	0	0	0	+?	0	0	0
Temperature (C°.), highest value during week in question	(Before)	38·0	36·8	37·6	37·2	37·4	38·2	37·8	37·5	37·4	37·1	37·6
	(After)	37·9	37·0	37·1	36·9	37·1	36·9	37·1	37·4	36·9	36·5	36·9
Erythrocyte sedimentation rate	(Before)	35	59	10	32	80	110	92	72	25	25	39
	(After)	70	10	8	22	64	14	42	53	28	11	24
Hb per cent.	(Before)	77	60	79	84	75	85	76	77	67	79	63
	(After)	79	76	—	82	71	82	71	75	85	86	92
Eosinophils per c.mm.	Before	410	111	175	250	—	61	125	126	90	172	170
	Highest value	5,810	224	297	475	748	177	240	616	341	462	726
	After	1,633	43	297	475	748	33	78	616	341	462	726
Serum cholesterol (mg. per cent.)	(Before)	230	113	—	278	203	117	187	265	191	140	155
	(After)	272	—	—	298	—	246	265	300	185	269	315

0 = None. +? = Uncertain. + = Moderate. ++ = Severe. — = No Determination.

ADDITIONAL NOTES TO TABLE

Case 1. The patient had been in the ward continuously for 168 days before the propyl-thiouracil medication was started. He had been treated with myocrisin 270 mg. and blood transfusions 400 ml. × 4 without any remission. He was still febrile. The sedimentation rate was 62 at the beginning and after the therapy 73 mm. Then he was given cortone 2·850 g. during 23 days; the remission was moderate, and sedimentation rate fell from 75 to 19. The second day after this therapy was stopped the articular pains became aggravated and the temperature rose. Seven days after stopping cortisone the thiouracil medication was started. After 2 weeks' thiouracil medication (propyl thiouracil 0·1 × 3) the patient was without fever, the sedimentation rate 54; the Hb per cent. had risen during this time from 77 to 85. The patient himself found his joints as good as during the cortone therapy. As the number of the eosinophils per c.mm., however, had risen as high as to 5,810, the daily amount of thiouracil had to be diminished, and only 0·1 g. was given every second day. At this time a tonsillectomy was also performed; the RA symptoms were at once aggravated and the patient again became febrile.

Cases 2 and 6. Both these patients had slight symptoms of thyrotoxicosis.

Case 10. In this case there was typical thyrotoxicosis (but no signs of exophthalmic goitre or struma nodosa).

However, observations showing quite contrary results have also been published. Rheumatoid arthritis has developed simultaneously with the symptoms of hypothyrosis after a resection of the thyroid (Cushing, 1937; Lundgren, 1943; Kirstein and Lövgren, 1937; Thomas, 1933). Correspondingly, different observations have been reported on the effects of thyroid medication upon the course

of rheumatoid arthritis. For example, Hall and Monroe (1933) observed a favourable action in 16 per cent. and Rawls and others (1938) in 20 per cent. of their cases. Copeman (1946), on the other hand, found that thyroid medication can have disadvantageous reactions in severe rheumatoid arthritis.

The early inhomogeneous studies perhaps suggest the conclusion that a dysfunction of the thyroid, in one direction or another, may possibly facilitate an aggravation of rheumatoid arthritis. In any case, it is difficult to assume that thiouracil, through reducing the secretion of the thyroid, would have a favourable effect on rheumatoid arthritis. Seven of the patients were euthyrotic, and only one of them had a manifest thyrotoxicosis (two had slight but not definite symptoms).

Particular attention must be paid to the effects of thiouracil on the *adrenal* glands which play a central role in the problems of rheumatology. It has been demonstrated experimentally that the administration of thiouracil effects destruction and atrophy in the adrenal cortex (Arvy and Gabe, 1946; Deane and Greep, 1947; Florentin and others, 1947; Riker and Wescoe, 1945). Lesions have also been observed in the medulla (Arvy and Gabe, 1946). Clinical observations which confirm these experimental findings have also been reported. An inhibition of the eosinopenia which normally follows an injection of adrenaline—which inhibition is regarded as a sign of the insufficiency of the adrenal cortex—has been observed to occur in patients in the course of thiouracil medication (de la Balze and others, 1951). The eosinophilia occurring in connection with thiouracil treatment may also be thought to depend on a hypofunction of the adrenal glands.

The results of several investigators, therefore, suggest that *thiouracil medication reduces the hormone output of the adrenal cortex* (and possibly also that of the medulla). Accordingly, the action of thiouracil would be deleterious in rheumatic disease, if the view often presented that factors which stimulate the function of adrenal cortex—as various forms of stress, etc.—act favourably on this disease. *However, there are several facts which suggest that an active rheumatic state is connected, on the contrary, with a potent function of the adrenal cortex, whereas factors exerting a favourable action on rheumatoid arthritis are evidently connected with a suppressed function of the adrenal glands.*

As is well known, Selye (1947) attributes a central role in the pathogenesis of rheumatic conditions to an increased excretion of mineralocorticoids as a consequence of various " stresses ". It has also been clearly shown clinically that " stresses " stimulating adrenocortical function cause an exacerbation of the symptoms of rheumatoid arthritis. Thus, it has been demonstrated that cold, damp weather, mental and physical strain, as well as acute febrile infections (Järvinen, 1951) generally aggravate the clinical picture of rheumatoid arthritis and may serve as predisposing factors in its aetiology. This view is supported also by the finding that the active stage of rheumatoid arthritis is connected with eosinopenia (a sign of the stimulation of the adrenal function), whereas the spontaneous recovery of the disease is evidently characterized by eosinophilia (Järvinen, 1950a).

As mentioned above, signs of reduced adrenal (adrenocortical) activity may,

on the other hand, be demonstrated in connection with the rapid recovery of rheumatoid arthritis as effected by certain factors, such as severe jaundice, protracted starvation, toxic drug reactions, state of the organism after general anaesthesia, and massive administration of cortisone.

A severe jaundice—in general, the Meulengracht value has to rise to values like 1 : 70-1 : 90 before a recovery from rheumatoid arthritis is effected, whether the jaundice is due to stone, tumour, or hepatocellular factors (Ahlberg, 1939; Lövgren, 1945)—is characterized by hypotonia, bradycardia, subnormal temperature, and a tendency to leucopenia, i.e. by symptoms indicating vagotonia, which suggests a reduced adrenal function. The same symptoms occur in protracted starvation which has also been observed to have a curative action on rheumatoid arthritis (Hench, 1949). The view that the adrenal function is suppressed in these conditions is supported also by histological changes in the adrenals of patients who have succumbed to starvation. These changes indicate an exhaustion (Klinge, 1949).

The symptoms of rheumatoid arthritis disappear rapidly in connection with some drug reactions of toxic character. This is observed most often during gold-salt treatment, but it has occurred also in connection with sulphonamides (Virkkunen, 1947) and cincophen (Rawls, 1939), and also with transfusion complications (Appelqvist and Holsti, 1947). The recovery of the joint symptoms is intimately connected with the development of hypotonia and eosinophilia, as is evident from studies made on gold-salt reactions (Järvinen, 1946). Again, these signs suggest rather an inhibition than a stimulation of the adrenal glands.

The effects of sulphonamides on the adrenal glands have also been studied experimentally, and several investigators have found that the adrenal glands of experimental animals are reduced in size during sulphonamide medication (Riker and Wescoe, 1945) as they are during the administration of thiouracil. A similar action on the endocrine system is also suggested by the fact that both of these compounds are strumogenic, both reduce the basal metabolic rate, and both raise the serum cholesterol level (as also does cortisone), which level has a tendency to fall in active rheumatoid arthritis. Some sulphonamide drugs—salazopyrin—have also given results of some value in the treatment of rheumatoid arthritis (Svartz, 1948).

The relief of the symptoms of rheumatoid arthritis, which is often observed after general anaesthesia and which lasts for a few days (Hench, 1949), may, according to the writer's view, be regarded as connected with an exhaustion of the adrenal cortex after the anaesthesia and not with a protracted hyperfunction.

The massive administration of cortisone which effects a rapid temporary cure of the symptoms of rheumatoid arthritis has been observed to produce atrophy of the adrenal cortex in experimental animals (Stebbins, 1950; Antopol and others, 1951; Nichols and Miller, 1949). This corresponds with the clinical observations in man of a decreased excretion of 17-ketosteroids during the massive administration of cortisone (Wilkins and others, 1951). This effect is possibly due to a reduction in the mineralocorticoid secretion and not to an extra supply of glucocorticoids (cortisone). An increase of the secretion of glucocorticoids, even to a pathophysiological extent, does not seem to have any curative effect on rheumatoid

arthritis, nor even to be able to prevent its onset. This is suggested by work on the interrelations of rheumatoid arthritis and diabetes mellitus (Järvinen, 1950b).

The symptoms of rheumatoid arthritis do also sometimes disappear in connection with pregnancy. However, this phenomenon is by no means regular. For instance, there have been among the patients of our clinic during years 1934-1948 four women suffering from rheumatoid arthritis while pregnant in the fourth to the eighth month. In all of these, a temporary exacerbation of the disease occurred during pregnancy. (In eight women rheumatic fever began in the third to the ninth month, exhibiting articular symptoms, and in four the onset occurred just before delivery.) An assessment of the action of the different hormonal factors is rather difficult, as pregnancy produces thorough changes in the hormone equilibrium as a whole. It is possible that also the secretion of the adrenals varies individually and according to the stage of pregnancy.

Conclusions

Although the present cases of rheumatoid arthritis which were treated with thiouracil were closely observed, a definite assessment of the practical value of thiouracil in the treatment of patients suffering from rheumatoid arthritis cannot yet be made, on account of the paucity of the material. An estimate of the results is difficult because of the fluctuating character of the disease. However, the results were rather marked in some cases, and it is worthy of note that this treatment seems to have a mechanism of action—e.g. on the adrenal glands—similar to that of the most important agents acting favourably on rheumatoid arthritis.

Summary

Ten patients suffering from rheumatoid arthritis were given thiouracil in doses varying from 7·8 to 51·6 g. during a period of 17 to 86 days, under hospital control. In eight of the cases, a distinct improvement was observed during this treatment; in five of these the recovery was rather marked.

The discussion is chiefly devoted to the suppression of the functions of the adrenal glands (adrenal cortex) which was due to thiouracil medication, and to its possible role in the cures observed. Signs suggesting adrenocortical hypofunction are pointed out in connection with those conditions known to effect a rapid recovery from this disease, such as severe jaundice, protracted starvation, toxic drug reactions, general anaesthesia, and treatment with cortisone. Agents which bring about an increased function of the adrenal cortex are regarded as aggravating the symptoms of rheumatoid arthritis.

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L'emploi du thiouracil dans l'arthrite rhumatismale

RÉSUMÉ

Dix malades atteints d'arthrite rhumatismale furent traités par thiouracil en doses variant de 7,8 à 51,6 g. pendant des périodes de 17 à 86 jours, sous le contrôle hospitalier. Au cours de ce traitement on nota une amélioration appréciable dans huit cas et dans cinq d'entre eux le rétablissement fut assez marqué.

On discute surtout la suppression de la fonction cortico-surrénale à la suite de la médication par le thiouracil et on considère son rôle dans les guérisons observées. On signale les manifestations qui suggèrent une diminution de la fonction cortico-surrénale, ce qu'on interprète à la lumière des facteurs qu'on sait capables d'effecteur un rétablissement rapide, tels qu'ictère grave, famine prolongée, réactions toxiques aux substances médicamenteuses, anesthésie générale et traitement par la cortisone. Les agents susceptibles d'augmenter la fonction de l'écorce surrénale sont considérés capables d'aggraver les symptomes de l'arthrite rhumatismale.

El empleo de tiouracil en la artritis reumatoide

SUMARIO

Diez enfermos con artritis reumatoide fueron tratados con tiouracil cuya dosis variaba de 7,8 a 51,6 g. durante períodos de 17 a 86 días, bajo control hospitalario. Durante el tratamiento se notó en ocho casos una mejoría distinta, bastante pronunciada en cinco de ellos.

El objeto principal de la discusión es la función córtico-suprarrenal que queda suprimida a consecuencia de la medicación con tiouracil, así como el papel de éste en las curaciones observadas. Se señala las manifestaciones que sugieren una diminición de la función córtico-suprarrenal en relación con los factores que se sabe capaces de producir el restablecimiento del enfermo, como ictericia grave, inanición prolongada, reacciones medicamentosas tóxicas, anestesia general y tratamiento con la cortisona. Se considera que los factores que hacen aumentar la función de la corteza suprarrenal también agravan los síntomas de la artritis reumatoide.

HEATING THE KNEE JOINT

BY

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It is generally conceded that radiant heat is less effective than diathermy for heating joints. We have made some observations on this point in the knee joint in the course of other studies and present here our methods and results which may be of value to those who are interested in measuring joint temperatures and assessing the effectiveness of treatment.

Methods

The left leg of one subject was used for each test. The subject was seated with the leg hanging vertically. Skin temperature was recorded with two wire thermocouples made of 30 s.w.g. constantan and 47 s.w.g. copper (Whyte, 1951) held in place by the springiness of the wire leads, which were fixed more remotely to skin with adhesive plaster. This type of thermocouple records skin temperature with less than 0·5° C. error even in the presence of radiant heat. The intra-articular temperature was recorded with a needle thermocouple passed through an area anaesthetized with a small amount of 2 per cent. novocaine on the antero-medial side of the joint. The needle thermocouple was made of 47 s.w.g. copper and constantan wires soldered to the tip of a steel needle 0·5 mm. in diameter (Whyte and Reader, 1951). It is accurate to 0·1° C. and is not affected by radiant heat. The thermocouples were connected to a reference junction in a thermos of water maintained by a heating coil at about 37° C., and through a switch box to a galvanometer whose deflection was shown by the movement of a beam of light on a scale. The thermocouples were calibrated by water immersion; 1° C. gave a deflection of 1 cm.

Two sources of radiant heat were used: long-wave infra-red radiation from an 800-watt Sollux dark-source, and short-wave infra-red radiation from a 1,000-watt tungsten filament lamp.* The intensity was measured with the thermoradiometer of Evans and Mendelssohn (1946).

Diathermy was supplied from a Siemen's " Ultratherm " apparatus operating at a fixed wavelength of 6 metres and a frequency of 50 megacycles, with a filament voltage of 20. An inductothermy coil was wound round the knee.

Results

Radiant heat was applied to the front and medial side of the knee, first 1·0 pyron (1·0 g. cal./sq. cm./min.) of long-wave infra-red for 30 min., then after a 30-min. rest 2·0 pyrons of short-wave infra-red for a further 30 min. The results are shown in the Figure. The joint temperature fell slowly from 33·6 to 33·2° C. during the preliminary period of 15 min. and then continued to fall at this rate to 32·9° C. in the first 10 min. of heating, in spite of an abrupt rise of skin temperature to about 40° C. The joint temperature then rose and continued to do

* We are indebted to Hanovia Ltd., Slough, for the loan of this lamp.

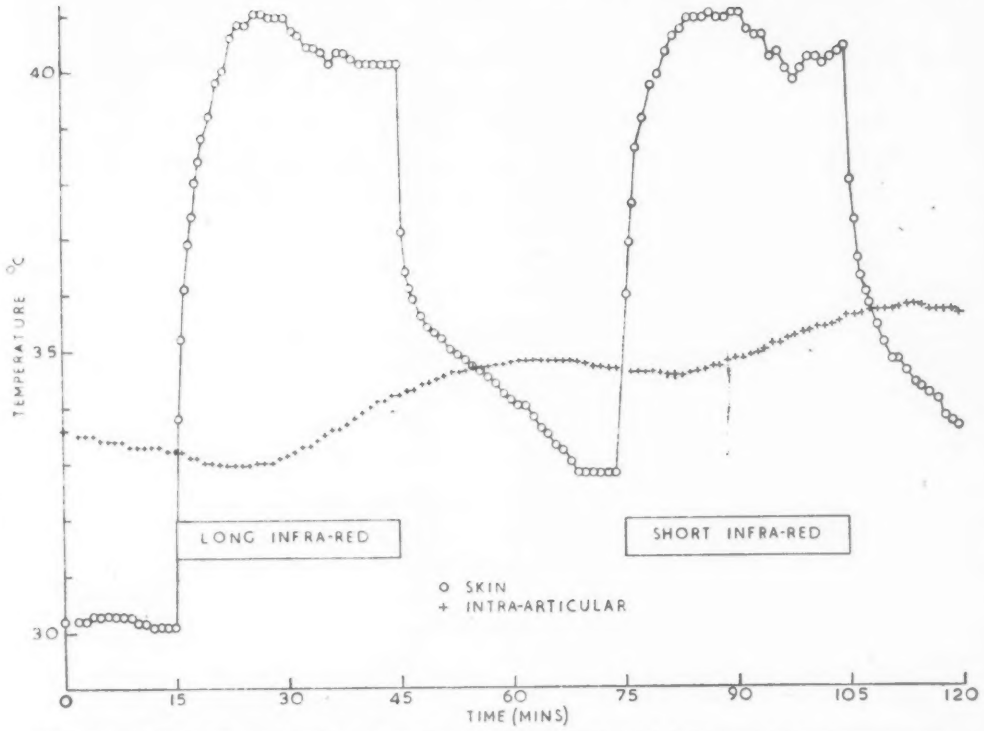

FIGURE.—Effect of application of radiant heat on skin and intra-articular temperatures of knee joint.

so for 20 min. after the radiation had been stopped, reaching a maximum of 34·8° C. A similar effect was produced by the short-wave infra-red radiation.

The Ultratherm was used for 30 min. on another occasion, the thermocouples being removed during the period of heating. The initial skin temperature was 31·4° C. The joint temperature reached its peak 6 min. after heating was stopped. The effects of the three methods of heating are shown below:

Method of Heating	Joint Temperature (° C.)		
	Initial	Maximum	Rise
Long infra-red	33·2	34·8	1·6
Short infra-red	34·7	35·8	1·1
Diathermy	35·0	37·7	2·7

Discussion

Diathermy is the best of the three methods used here for heating the knee joint. The fact that diathermy caused the joint temperature to rise above the normal temperature of blood is an indication of deep penetration by this form of heat. On the other hand, the delayed and poor response to radiant heat can be interpreted to mean that infra-red radiation, even of the most penetrating type such as that

given by a tungsten filament lamp (Hardy and Muschenheim, 1936), has no direct effect on the joint. When radiation is applied to the knee the heat is absorbed by the skin and superficial tissues and is carried away by the blood without directly influencing to any appreciable extent the temperature of the underlying joint. However, the absorption of heat and the consequent increase in blood flow lead to gradual warming of the whole leg, as a result of which the temperatures throughout the limb, particularly in the centre, approach the temperature of the blood. Thus, the application of moderate amounts of heat to the whole limb is probably more efficient than applying intense heat restricted to the region of the joint when radiant heat, hot-water bottles, or other non-penetrating forms of heat are used. The most that can be hoped for with these methods is to raise the joint temperature to 37° C. or slightly more. The most efficient heating would be given by warming the whole limb at the same time as applying diathermy to the knee.

Horvath and Hollander (1949) recorded an abrupt fall in joint temperature when hot packs were applied to the knee, and the opposite effect was produced when cold packs were used. They attributed these changes to vascular reflexes. No such changes were observed in the present study.

Summary

The changes in temperature produced by different methods of heating were measured by thermocouples.

Diathermy was more effective than either long- or short-wave infra-red radiation.

The effect of radiant heat on the joint is thought to be determined mainly by the changes produced in the whole limb.

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Chauffage de l'articulation du genou

Résumé

Les variations de la température produites par de différentes méthodes de chauffage furent mesurées à l'aide des couples thermoélectriques.

La diathermie s'est montrée plus efficace que les rayons infrarouges à onde grande ou courte.

On considère que l'effet des rayons thermiques sur l'articulation est déterminé surtout par les modifications survenant dans le membre entier.

Calentamiento de la articulación de la rodilla

Sumario

Las variaciones de la temperatura producidas por diferentes métodos de calentamiento fueron medidas por medio del par termoeléctrico.

La diatermia se mostró más eficaz que los rayos infrarrojos de onda larga o corta.

Se considera que el efecto de los rayos térmicos sobre la articulación se debe sobre todo a las modificaciones que sobrevienen en el miembro entero.

A METHOD OF MEASURING SWEAT FROM THE HANDS

SOME RESULTS IN RHEUMATOID ARTHRITIS

BY

A. WOODMANSEY

From the Royal Bath Hospital, Harrogate

(RECEIVED FOR PUBLICATION DECEMBER 7, 1951)

Sweat is well known to vary in composition and amount over different areas of the body. A wide range of values is found in sweat from corresponding areas in different individuals, and in our experience even from the same subject at different times under apparently the same conditions.

The extent of this range is in itself a matter of considerable interest and invites fuller investigation of the sweat in conditions of disease, as, for instance, in rheumatoid arthritis, since the impression exists among clinicians that clammy hands are more common in arthritic patients than in normal subjects. An additional incentive to further research arises from the work of Conn and Louis (1950), who claim that the concentration of sodium and chloride in thermal sweat is governed by the activity of the adrenal cortex, which may be implicated in diverse pathological conditions.

A distinction is usually drawn between insensible sweat, which is largely due to evaporation of water through the skin, and sensible sweat, the visible secretion of the sweat glands under conditions of thermal stimulation. Sweating on the palms and soles is stated to be independent of thermal stimuli, unless these are very strong, but to be regulated by mental stimuli (Kuno, 1934).

Much of the work of previous investigators has been done on the profuse sweat of the naturally or artificially overheated body. McSwiney (1934) enclosed his subject in a rubber suit provided with tubes to run off the sweat, and placed him in a heat cabinet for periods up to an hour. Dill and others (1938) experimented on members of the Harvard Desert Expedition. Moisture was estimated from the loss of body weight corrected for loss of moisture from the lungs. The solids secreted in the sweat were obtained by washing body and clothes. Conn and Louis provoked sweating by exposing the body to a hot (95° F.) humid atmosphere, samples being collected from the abdomen and hand plus forearm. Locke and others (1951) induced sweating by a high room temperature (32° C.), and by placing one arm in hot water. The sweat was obtained by enclosing the non-immersed arm in a waterproof envelope and weighing the moisture delivered, allowing for adherent moisture. Kuno describes very elaborate methods used in his "perspiration chamber" for obtaining the insensible perspiration from small areas of the body, by the use of collecting covers drawing the air through $CaCl_2$ tubes; his portable equipment employed a hair hygrometer. Darling (1948) measured the

rate of insensible sweating on an area of the palm of the hand by absorption on a weighed gauze pad (covered with plastic sheeting sealed to the skin), and afterwards dissolved out the chloride, urea, and other substances for analysis.

After consideration of these and other techniques with which tentative experiments were made, the following method was evolved as suitable for observing rapid changes in sweating behaviour under various therapeutic or other special conditions. (Woodmansey, 1951). It is simple and convenient to perform, and the necessary apparatus is readily available. It can be carried out at any time on any patient, and does not rely on a room of constant temperature, though this, of course, enables a greater degree of standardization.

The rate of moisture elimination is measured on a small area of the palm and/or dorsum of the hand or on the thumb. Both hands are taken for the estimation of salt and urea in order to get sufficient for accurate analysis. Other constituents of sweat have not been dealt with in this study.

The measurement of moisture is carried out on a smaller area than is used for the estimation of solids. This does not matter because we are not now considering the tonicity of the sweat or the energetics of sweating.

Method

The patient is kept under resting but not basal conditions. No restrictions of dietary salt or fluids have yet been imposed in our experiments, because, as Newburgh and Johnston (1942) and others have shown, moderate dehydration or hydration of the body, or small variations of salt in the diet, have no effect on the insensible loss of water.

The patient sits in a room thermostatically controlled as closely as possible to 18·3° C. (65° F.). The hands are well washed in tepid tap water, followed by distilled water, and lightly dried. They are then rested sideways on a clean towel spread over the knee or in large beakers to avoid loss if more actively sweating. After a period of an hour, each hand in turn is well rinsed in 500 ml. tepid ammonia-free distilled water in a tall beaker by immersing to the first crease on the wrist or to some other predetermined mark, the fingers being actively moved to and fro. Half of the washing water (250 ml.) is evaporated to small bulk. The chloride in it, determined by the ordinary method, represents the amount of salt excreted by one hand in an hour (Na and K have not yet been determined separately). The other 250 ml. is incubated with a crushed urease tablet and 2 ml. toluene. On distillation the first 100 ml. contain all the ammonia which is estimated colorimetrically after the addition of Nessler solution. This result represents the amount of urea (plus a little ammonium salt) from the sweat of one hand.

In view of their different control mechanisms, an attempt has been made in a few cases to determine separately the palmar and dorsal secretions of salt and urea. This was done by carefully moving the half-submerged hands in two shallow dishes of water, palm upward in one and dorsum upward in the other, the washings being analysed as above.

The rate of (moisture) sweating from the thumb or from a small area (about 4 × 4 cm.) of the palm or dorsum of the hand is determined by passing $CaCl_2$-dried air through a collector into a weighed $CaCl_2$ U-tube, and finally through a bubbler to indicate the air flow to an electric or water pump (or aspirator bottles). The flow should be rapid enough to prevent visible condensation. 10 to 30 min. flow is sufficient. The weighed moisture is calculated to an hourly rate.

The volumes of the hand and thumb (measured by displacement) are recorded for further consideration if required. Skin temperatures of palm, dorsum, thumb, and forehead are taken periodically through the test.

Apparatus.—The collector for palm and dorsum (Fig. 1) is made from a short bottle by grinding off the base (this requires care) or from $\frac{1}{8}$″ Perspex in round or square box form. Perspex is easy to work with simple tools, and can be bent over a small flame. A scrap of the material dissolved in ethylene dichloride is used as cement. Inlet and outlet glass tubes passing through rubber corks are also required. A sponge-rubber washer (shown in the diagram) $\frac{1}{4}$″ thick, rendered non-porous with rubber solution, is not usually required. It is better to hold the collector in position by hand during the test than to tie it on.

The collector for the thumb (Fig. 2) is even easier to make; this consists of a piece of glass

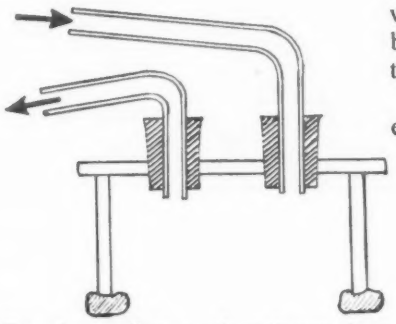

FIG. 1.—Collector of moisture from palm or dorsum.

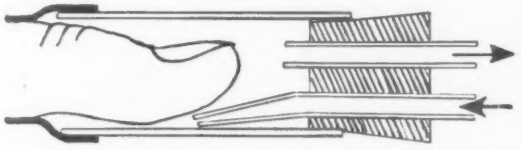

FIG. 2.—Collector of moisture from thumb.

tubing about 3″ long and 1 or $1\frac{1}{8}$″ in diameter to fit loosely over the thumb. The long inlet tube (flattened to fit under the thumb) and short outlet tube pass through the rubber cork at one end. A short length cut from the thumb of a discarded surgical glove stretched over the other end makes a perfect seal without constriction.

Results

Tests were made with 42 rheumatoid arthritic patients selected at random, and eleven normal subjects. Clinical data of the former were available, but as these showed no correlation with the sweat figures they have been omitted. The scatter diagram (Fig. 3) shows the wide range of values obtained and confirms the observations of others with regard to the output of moisture and salt. Indeed, the NaCl column should have been extended to show a few isolated points lying far beyond the limits of the scale; the highest was, in fact, 13·6 mg. Such cases may prove to be of particular interest.

The urea output varies less than that of salt, for whereas the points on the NaCl scale are more or less evenly

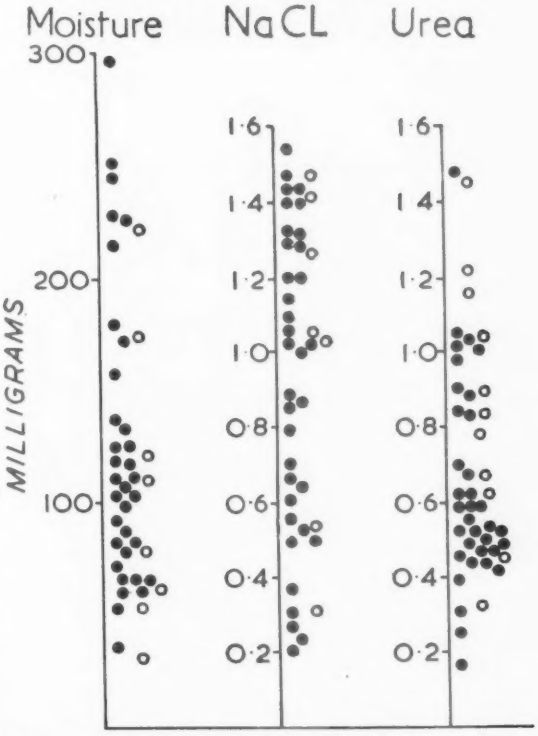

FIG. 3.—Results in mg. moisture per hour from the thumb, and mg. NaCl and Urea per hour from one hand.
Black dots—rheumatoid arthritic patients.
Circles—normal subjects.

dispersed between 0·2 and 1·6 mg., the urea values tend to cluster in the 0·4 to 0·6 mg. region.

The wide variation between maximum and minimum amounts of salt and urea in insensible sweat from the hands of an ordinary healthy individual taken on a number of occasions on the same and on different days is shown below. The circumstances of these variations still require elucidation.

NaCl		Urea	
Max.	*Min.*	*Max.*	*Min.*
1·37	0·56	1·00	0·53

In eight cases (mostly normals) where the palmar and dorsal washings were kept separate, the results were as follows:

Case No.	Both Palms		Both Dorsi	
	NaCl	Urea	NaCl	Urea
1	2·60	1·22	1·40	0·65
2	0·70	0·44	0·35	0·34
3	2·03	0·56	0·78	0·39
4	3·05	1·07	1·20	0·44
5	1·45	0·81	0·80	0·33
6	1·03	0·97	1·00	0·72
7	0·75	0·46	0·32	0·18
8	3·30	2·25	0·85	0·97

The excretion of both constituents is thus greater from palm than from dorsum. Similarly, whenever measurements of moisture were made, that from the palm was greater than that from the dorsum, but there was no regularity in the ratio.

The technical method described above is at present being used in an attempt to throw light on such problems as

(*a*) the apparent vagaries of insensible sweating,

(*b*) the differences in sweat behaviour between normal persons and rheumatoid arthritic patients,

(*c*) what changes occur when a thermal stimulus is applied or when hormonal or other therapy is being given.

Summary

A simple method is described for the estimation of moisture, salt, and urea in insensible sweat from the hand.

Figures are given, showing the wide range of values to be expected in normal subjects and in rheumatoid arthritic patients.

I wish to thank Professor A. Hemingway for his encouragement in the investigation, Professor S. J. Hartfall for his continued interest, and for the provision of clinical cases, and Dr. D. H. Collins for much helpful advice.

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Une méthode pour mesurer la sueur des mains

RÉSUMÉ

On décrit une méthode simple pour déterminer l'humidité, le taux du sel, et celui de l'urée dans la sueur imperceptible des mains.

On présente des chiffres montrant la gamme étendue des valeurs qu'on peut obtenir chez les sujets normaux et les arthritiques rhumatisants.

Un método para medir el sudor de las manos

SUMARIO

Se describe un método sencillo para determinar la humedad, la sal, y la urea en el sudor imperceptible de las manos.

Se presenta cifras mostrando la gran amplitud de las variaciones de los valores tanto en los sujetos normales como en los enfermos con artritis reumatoide.

BOOK REVIEWS

Medical Disorders of the Locomotor System. By Ernest Fletcher, M.D., M.R.C.P. Second edition, 1951. E. and S. Livingstone, Edinburgh. Pp. 884. 60*s*.

When this book first appeared in 1947 it received a full and favourable review in this Journal (*Annals of the Rheumatic Diseases*, 1946, **5**, 225). It was claimed that the book was " a most important contribution to the literature of the subject ", and the appearance of this second edition is ample justification of this opinion.

There is no doubt that this is a good book which every practitioner in this field of medicine must add to his library.

The new edition is an improvement on the first edition, and has grown from 625 to 884 pages; its usefulness as a work of reference has been greatly helped by the vastly improved index. Here an entirely new " author index " has been added, extending over 10 pages, while the " subject index " has increased from 8½ to 18 pages.

Apart from complete revision, new chapters and sections have been added by new contributors. Professor S. L. Baker has made an excellent contribution on " The Anatomy and Physiology of Bone ", and Dr. J. Barrie Murray on " Psychiatric Aspects of Locomotor Disorders ". Dr. G. D. Kersley has contributed a section on Hydrotherapy, and Professor C. Rimington one on " Synovial Mucin ". Dr. H. J. Gibson is responsible for " Laboratory Findings in Locomotor Disorders ".

Dr. Fletcher himself makes a valiant attempt at the impossible in trying to keep up-to-date with the enormous literature which mushrooms up around us on cortisone and ACTH. His additions include an up-to-date survey of the work done on synovial fluid and the collagen diseases. It is with justifiable pride that he welcomes his son, Anthony Phillips Fletcher, as a new contributor who writes a comprehensive chapter on the difficult subject of " Pain ".

In a book so full and detailed, it is surprising to find so little mention of the treatment of the secondary anaemia encountered in so many cases of rheumatoid arthritis which can present so difficult a therapeutic problem. There would seem to be no mention of intravenous therapy at all, and the exercises advised for this type of case are not graduated as carefully as modern therapy seems to require.

It is extraordinary, too, how wide a variation of opinion seems to exist among different authorities regarding the optimum position for ankylosis of various joints and the period of time for which any one joint may be immobilized without producing an unwanted fixation.

The first edition was considered to be " well printed and lavishly illustrated ", but the number of illustrations has now been increased from 261 to 377. The printing and production is typical of the excellent standard which we have come to expect of any publication from the house of E. and S. Livingstone of Edinburgh. The new contributors and the new revision maintains the high standard reached in the first edition, and Dr. Ernest Fletcher is to be congratulated on a worthy achievement.

His eagle eye, however, seems to have missed one small erratum carried over from the first edition. On page 349, in line 5 of the final paragraph, he states that " a *wealthy* country like ours should . . ., etc.". Let us hope that when the third edition of this book is reviewed, it will be found unnecessary to change this quaint old-time phrase.

M. PATTERSON, M.D., F.R.C.P.(Edin.).

Home Care in Rheumatoid Arthritis. Issued by the Medical and Scientific Committee of the Arthritis and Rheumatism Foundation of New York. Pp. 24. 10 cents; 1*s*.

This pamphlet has been prepared for distribution by doctors to patients suffering from rheumatoid arthritis. It is intended to supplement the physician's work, not to replace it, and with this object, appropriate physiological exercises, designed to prevent and correct deformity and muscular weakness and wasting, are fully described. The place in the treatment of rest, the importance of proper posture, suitable mattresses in bed, and the best type of chair to use when up, receive attention. Simple apparatus which can be used in the home for treatment by heat to relieve pain and stiffness, the temperature which is most suitable and the duration of treatment, locally or by means of such baths as are possible in the home, are fully described. Throughout, the necessity of medical supervision in the selection of the appropriate exercises and treatment is emphasized; and doctors, especially those in country practice or where hospitals are not within easy reach or domestic circumstances make them difficult of access, will certainly find it very helpful in the management of their rheumatoid cases and probably in certain other conditions.

The pamphlet may be obtained from the Arthritis and Rheumatism Foundation, 23 West 45th St., New York 19, N.Y., U.S.A. C. W. BUCKLEY.

La Spondylarthrite Ankylosante. By J. Forestier, F. Jacqueline, and J. Rotes-Querol. 1951. Masson, Paris. Pp. 330, 143 figs. Fr. 2,650; 58*s*. 6*d*.

This book contains a detailed clinical account of ankylosing spondylitis, followed by sections on morbid anatomy and on treatment. The clinical section is based, in the main, on a series of 200 cases, some of them studied over very long periods, and is of great value for its analysis, not only of spinal, sacro-iliac, and peripheral symptoms, but also of those more bizarre manifestations that make this condition so interesting to the rheumatologist. There are good chapters on modes of onset and progress, and on clinical forms —the authors recognize both a *forme latente* and a *forme fruste*. Rather surprisingly, they found psoriatic lesions in thirteen of their 200 cases, and they consider that this association is another variant.

Sacro-iliac joint affection was almost always found radiologically in their series, and *x* ray of this region is considered of great importance in diagnosis. The authors suggest that the onset of symptoms may precede the appearance of radiological signs by some months, and they also suggest that early sacro-iliac changes may be in rare cases reversible so that the joint returns to normal. Such a case is cited; but it seems to have been an odd and atypical one.

The section devoted to morbid anatomy is concerned both with the study of bony specimens and with autopsy findings. Particular attention has been paid to the structure and formation of the calcific bridging between vertebral bodies, here called *syndesmophytes*, which are considered to be an important radiological sign in the diagnosis and progress of the disease.

Because affection of the peripheral joints is the main reason for crippling deformity, the authors stress the importance of treating them as well as the spinal column. Radiotherapy, though of value in the relief of painful symptoms, probably does not affect the course of the disease: thorium *x* and radon are, in the authors' experience, of equal value.

The laconic and clear style, the numerous and technically excellent photographs and *x*-ray reproductions, and the extensive bibliography make this a good book both for reading and for reference. There is no doubt that this is a valuable contribution to our advancing knowledge of ankylosing spondylitis. B. E. W. MACE.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

H.M. KING GEORGE VI

The following messages have been received by the editors from rheumatologists abroad:

La Ligue Européenne contre le Rhumatisme vous prie accepter pous vous et vos membres l'assurance de notre vive sympathie et profondes condoléances à l'occasion de la mort de votre illustre roi. Ferond, Président.

Le Comité d'Administration et les Membres de la " Ligue Belge contre le Rhumatisme ", vivement émus par la décès du roi Georges VI, prennent une part très profonde au deuil qui frappe la nation britannique.

Ils me chargent de présenter au Comité et aux Membres de la " British Branch of the European League against Rheumatism " l'expression de leur très vive sympathie. Colinet, Secretaire-Général.

GENERAL MEETING, 1951

A general meeting of the Council was held at Barcelona on September 23, 1951. The President, Dr. W. S. C. Copeman, who was in the chair, gave the following address:

The Secretary-General of the Ligue Européenne will report on the work of the Ligue for these past two years during which I have had the honour to be its President. Therefore, I shall not go into details, but just venture a few remarks of a more general nature.

Part of the Ligue's work has been done in conjunction with the Ligue Internationale contre le Rhumatisme, of which it forms a not insignificant part.

In this connection I should like to mention the work done by both the European and Pan-American leagues to gain the official recognition of the World Health Organization, which was obtained in February, 1950, after the fifth Session of the Executive Board of the W.H.O.

Because of economic conditions we have not yet succeeded in establishing the Expert Committee on Rheumatic Diseases, but I know that the President of the Ligue Internationale and Professor Walthard (*Geneva*) are working intensively on this problem.

The first edition of the Yearbook of the Ligue Internationale was published with prefaces in English, French, and Spanish by the National Danish Association against Rheumatic Diseases, and during the course of

this meeting this whole question of further publication and finance will be discussed thoroughly. Lastly, I should like to mention that the financial position of the Ligue Européenne can be considered satisfactory, as is shown by the statement of accounts already circulated to all councillors. The Secretary, Dr. Kalbak, who has worked so hard and so successfully for us during these years, will be presenting the accounts on behalf of the Treasurer. This is an unfortunate necessity, as Mr. Ove de Bornemann's health has not permitted him to be with us at this council meeting, and I am afraid that in the future we shall be deprived of his valuable assistance as treasurer. I am sure you will all agree that this is most regrettable and that we must send him our most cordial thanks for all he has done for us! (Applause.)

It has been a great pleasure to me to be President of the Ligue Européenne during this period in which rheumatological research has progressed so brilliantly. May I express the hope that the coming two years will show still further progress in this science, bringing positive results for the aid of the many patients who are suffering from rheumatic diseases everywhere in the world.

The following councillors were present at the general meeting:

Austria:	Prof. K. Gotsch and Dr. W. Schindler.
Belgium:	Dr. M. Ory and Prof. W. Esser.
Czechoslovakia:	Not represented.
Denmark:	Dr. K. Jespersen.
Eire:	Not represented.
Finland:	Dr. P. Peltola.
France:	Prof. S. de Sèze and Dr. A. Thiers.
Great Britain:	Dr. G. D. Kersley.
Hungary:	Not represented.
Italy:	Prof. G. Sabatini and Prof. A. Masturzo.
Netherlands:	Not represented.
Norway:	Not represented.
Portugal:	Prof. A. Flores and Dr. A. Teixeira.
Spain:	Dr. R. Cirerá Volta and Dr. J. Grinda.
Sweden:	Dr. O. Lövgren.
Switzerland:	Prof. K. M. Walthard and Prof. A. Böni.
Turkey:	Not represented.
Yugoslavia:	Not represented.

The following executives were also present:

Secretary-General:	Dr. G. Edström (*Sweden*).
President Ligue Internationale:	Prof. E. Jarløv (*Denmark*).
Secretary-Treasurer Ligue Internationale:	Dr. W. S. Tegner (*Great Britain*).
	Dr. Mathieu-Pierre Weil (*France*).
	Dr. P. Barceló (*Spain*).
	Prof. L. Michotte (*Belgium*).
	Dr. K. Kalbak (*Denmark*).

Apologies for absence were received from Dr. M. Ferond (*Belgium*), and Mr. O. de Bornemann (*Denmark*).

The Chairman then asked the Secretary-General, Dr. Edström, to deliver his report:

During the two years that have passed since the Congress at New York in 1949, the work of the Ligue Européenne contre le Rhumatisme has mainly been dominated by the observations of Hench, Kendall, and their co-workers with regard to the effect of cortisone and ACTH on the rheumatic diseases. These new discoveries—the importance of which may be judged from the fact that Drs Hench and Kendall together with Prof. Reichstein from Switzerland received the Nobel Prize last year for their work—raised rheumatology to a level which has been of great advantage to all of us who are interested in this science.

Interest in the rheumatic diseases is steadily growing all over the world, and this has manifested itself in the increasing number of members in the organizations of the various countries, in the mounting number of articles on rheumatological subjects, and, not least in importance, in the high standard of their content, which is continuously improving. Here I should like to mention the *Annals of the Rheumatic Diseases*, which, in my opinion, has developed into a first-class journal. It is a pleasure to me to express officially how very well pleased the Ligue Européenne is with this journal, and, at the same time, to thank our British colleagues for their work in making this periodical inter-European as well as international. There is hardly any doubt that the *Annals* has also contributed to a great extent towards the happy development of inter-European teamwork amongst rheumatologists.

It is likewise pleasing to note that the many local scientific periodicals on rheumatology in the various European countries have also increased. I should particularly like to mention the *Revue du Rhumatisme*, the *Zeitschrift für Rheumaforschung*, and the *Revista Española de Reumatismo*.

Another sign of the growing importance of rheumatology is that in recent years professorships have been established one after the other all over Europe: this year has seen the inauguration of those of Professor Coste in Paris, Professor Michotte in Louvain, and Professor Masturzo in Naples.

Yet another expression of growing interest has been seen in the many national and local scientific meetings held in these past two years, all well attended, and scientifically profitable.

Besides being able to establish that scientific research work is growing steadily and that rheumatology is being accepted as a definite subject amongst physicians the world over, it is a great pleasure to me at this meeting to inform you that the number of member states in the European league has been increased from seventeen to nineteen; the Austrian league has become a member since the last congress, with Professor Gotsch as President, and Germany was also admitted only to-day.

The Secretary, Dr. Kalbak, then presented the

Statement of Accounts for the year 1950 on behalf of the Treasurer, Mr. de Bornemann, and this was unanimously approved by the meeting.

Under the item, New Elections, the chairman mentioned that only one proposal for the new president had been received, namely that from the Belgian league, suggesting Dr. Ferond. This proposal was unanimously accepted, and the other officers were also unanimously elected:

President:	Dr. M. Ferond (*Belgium*).
First Vice-President:	Dr. Pedro Barceló (*Spain*).
Second Vice-President:	Dr. J. Goslings (*Netherlands*).
Secretary-General:	Dr. G. Edström (*Sweden*).
Vice-Secretary-General:	Prof. L. Michotte (*Belgium*).
Secretary-Treasurer:	Dr. K. Kalbak (*Denmark*).

Dr. Kalbak was asked to combine the treasurership of the league with the secretaryship, since, as already mentioned, the Treasurer, Mr. de Bornemann, had decided not to stand for re-election.

LIGUE BELGE CONTRE LE RHUMATISME

EXECUTIVE COMMITTEE, 1952

President:
Prof. Regniers, 289 Martelaarslaan, Gand.

Vice-Presidents:
Prof. Esser, 11 Rue Charles Morren, Liége.
Prof. Michotte, 40 Rue d'Arlon, Bruxelles.
Dr. Ory, 26 Rue de la Paix, Liége.

Secretary-General:
Dr. E. Colinet, 48 Rue d'Irlande, Bruxelles.

Co-Secretary:
Dr. Et. Vereecken, 49 Onderbergen, Gand.

Treasurer:
Dr. E. Colinet, 48 Rue d'Irlande, Bruxelles.

SOCIETÀ ITALIANA PER LO STUDIO DEL REUMATISMO

SIXTH NATIONAL CONGRESS, 1952

The Italian Rheumatism Association will hold its Sixth Congress at Taormina, Sicily, on May 23 and 24, 1952. The following papers will be read:

PROF. S. PISANI, **Fibrositis and Allied Pathological Conditions.**

PROFS L. VILLA, C. B. BALLABIO, and G. SALA, **The Problem of Cortisone in the Rheumatic Field.**

PROF. C. MARINO-ZUCO, **Osteo-Arthritis of the Hip. Problems and Feasibility of Orthopaedic Surgery.**

Participation in the Congress is extended also to non-members. The subscription is L.1,000 for members, and L.2,000 for non-members. Each subscriber may submit two papers.

Subscriptions, together with papers and a résumé of not more than 200 words, should be sent to Prof. Tomaso Galli, Clinica Medica Generale, Università, Viale Benedetto XV, Genova.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, 1952

The International Federation of Physical Medicine is organizing an International Congress to take place at King's College, London, from July 14 to 19, 1952, under the local management of the British Association of Physical Medicine. Lord Horder has been appointed President, with representative committees to organize the Congress. The attractive programme deals with Physical Education in the promotion of Physical Fitness; Rehabilitation and Resettlement; Chronic Rheumatic Disorders; Electro-Diagnostic Methods, etc. The social programme is also well planned, and the Congress will be followed by a 5-day provincial tour to places of interest associated with the objects of the Congress, including the Universities of Oxford and Cambridge.

Further information and details of the arrangements may be obtained from the Honorary Secretary, Dr. A. C. Boyle, British Association of Physical Medicine, 45 Lincoln's Inn Fields, London, W.C.2.

HEBERDEN SOCIETY

ANNUAL REPORT, 1951

The Society has again had a most successful year of work. During the year there were five resignations and these vacancies were filled by five admissions. The Executive Committee recommended, and the Annual General Meeting endorsed, the inauguration of Associate Membership to allow admission of members of the profession of junior status, and three associate members were duly admitted; there is, however, still a considerable waiting list for membership. Professor E. C. Kendall, who gave the Heberden Oration in 1951, has been elected an Honorary member of the Society. Dr. J. A. Cronin has succeeded Dr. J. M. Twhigg as an *ex-officio* Hon. Corresponding Member, as the new Chairman of the New Zealand Rheumatism Council.

At a meeting held at the Westminster Hospital, on January 24, Dr. J. H. H. Glyn (for Drs Copeman and Savage) exhibited a film on the therapeutic effects of cortisone, and many cases shown previously were demonstrated again after one year's progress, together with new cases (*Annals* (1951), **10,** 80).

On March 7, at the West London Hospital, a talk was given by Prof. Jiménez Diáz, Professor of Internal Medicine in Madrid University, and Director of the Institute of Medical Research, who showed a film on the effects of nitrogen mustard in rheumatoid arthritis (*Annals* (1951), **10,** 144).

At the Royal Free Hospital, London, N.W.3, on April 6, Dr. Ernest Fletcher discussed the results obtained by the intra-articular injection of cortisone, and illustrated his lecture by a film. Other speakers included Dr. E. G. L. Bywaters, Dr. J. F. Buchan, Mr. Charles Gray, and Mrs. V. David (*Annals* (1951), **10,** 189).

At a General Meeting held the same evening at the Ciba Foundation, 41 Portland Place, W.1, the Presidential Address was delivered by Sir Henry Cohen on "Some observations on the clinical analysis of pain especially in rheumatic disease" (*Annals* (1951), **10,** 221).

On April 11 at the West London Hospital, Prof. J. S. L. Browne, of Montreal, gave a talk on the use of ACTH and cortisone in the rheumatic diseases.

The Heberden Round took place in Edinburgh on May 10, by kind invitation of Prof. L. S. P. Davidson. Cases were demonstrated at the Royal Infirmary, and there was a conducted tour of the Rheumatism Unit, Northern General Hospital. A lecture on William Heberden the elder was given by Dr. Douglas Guthrie (*Annals* (1951), **10,** 217). Short communications were delivered by Prof. G. F. Marrian, Dr. W. R. D. Alexander, Dr. A. G. S. Hill, Dr. B. Cruickshank, Dr. A. P. Meiklejohn, Dr. J. L. Potter, and Dr. R. J. G. Sinclair (*Annals* (1951), **10,** 227).

At a meeting held at the Ciba Foundation on July 27, papers were given by Dr. W. H. Bradley, Drs E. G. L. Bywaters and A. St. J. Dixon, Dr. Fred Wrigley, Dr. D. A. Long,* and Dr. C. J. M. Clark (*Annals* (1951), **10,** 230).

The Heberden Oration for 1951 was delivered by Professor E. C. Kendall on "The Adrenal Cortex and Rheumatoid Arthritis" (*Annals* (1951), **10,** 453). The Old Library at B.M.A. House was filled to capacity and a distinguished audience included Mrs. Rebecca Kendall, Lord Webb-Johnson, Lord Horder, and Dr. A. S. Osborne (American Medical Attaché). Professor Kendall was presented by the President with the Heberden Medal, and the same evening an informal dinner party was given by the President at Claridge's Hotel at which Professor Kendall was guest of honour.

On December 7 and 8 at the Westminster Hospital (*see* p. 68), papers were given by Dr. M. R. Jeffrey,† Dr. Robert Moore, Prof. N. F. Maclagan, Drs. E. G. L. Bywaters and B. Ansell, and Dr. Bruce Cruickshank;† a symposium on cortisone and ACTH comprised papers by Dr. Norman Ashton, Dr. J. H. Kellgren, Dr. W. S. C. Copeman, Dr. H. F. West, Dr. E. G. L. Bywaters, Dr. G. D. Kersley, and Dr. J. J. R. Duthie.

At the Annual General Meeting the rules of the Society were altered to make provision for an "Associate Membership" of not more than twenty associates, three or four to be elected annually

* This paper was reported in full in *Annals of the Rheumatic Diseases* (1951), **10,** 427.

† These papers will appear in full in the **June, 1952, issue** of the *Annals*.

over a period of years; the following were accordingly invited to become associate members: Dr. A. St. J. Dixon, Dr. J. H. H. Glyn, and Dr. O. Janus. Rule 5 covers this new status of membership, and Rule 2 was also correspondingly amended. The ordinary membership subscription was increased from three to four guineas as from January 1, 1952. The Executive Committee's recommendation that Rule 4 should be altered to allow for this, in view of the increased cost of the *Annals of the Rheumatic Diseases*, was confirmed.

It was reported that the Heberden Medal had been recast to include a likeness of William Heberden the elder, through the generosity of the President, Sir Henry Cohen.

The President expressed the Society's deep appreciation of the "grant-in-aid" of £100 which had been made annually by the Empire Rheumatism Council; without such a grant the Society would be unable to balance its accounts, and it was much to be hoped that the Empire Rheumatism Council would continue to give this valuable financial support.

ANNUAL GENERAL MEETING, 1951

The Heberden Society met on December 7 and 8, 1951, in the Westminster Hospital Medical School, London. The President, Professor Sir Henry Cohen, was in the Chair. At the first meeting the following papers were read:

(1) Anaemia of Rheumatoid Arthritis,* by DR. M. R. JEFFREY (*Bath*).

(2) Generalized Osteo-Arthritis and Heberden's Nodes, by DR. ROBERT MOORE (*Manchester*).

From a study of 391 cases of osteo-arthritis, it had been possible to define a distinct clinical entity, for which the name "Primary Generalized Osteo-arthritis" is suggested. This group comprised 120 cases, 110 women and ten men. The characteristic feature of the syndrome was involvement of the hand joints, either Heberden's nodes or arthritis of the first carpo-metacarpal joints being present, and it occurred predominantly in the middle-aged, the average age of the women being 52 years, while that of the men was 50 years. There was no accurate association with the menopause.

The pattern of joint involvement was characteristic; Heberden's nodes were present on one or all fingers in most cases, and the first carpo-metacarpal joints were enlarged, deformed, and often partially subluxed, while the proximal interphalangeal joints were enlarged. The spine and hips were often limited in movement, while the knees were enlarged, effusions sometimes being present, and the first tarso-metatarsal joints were swollen. The joints tended to go through an initial acute phase of spontaneous onset, during which time they were acutely painful, swollen, and limited in movement, and this pain, especially in the hands, was aggravated by cooling.

In spite of the acute episodes in the course of the arthritis, constitutional disturbance was rare. Weight loss did not occur, the blood picture was normal, the blood sedimentation rate was normal in at least 50 per cent. of cases, the differential agglutination test (so often positive in rheumatoid arthritis) was negative, soft tissue lesions such as bursitis did not occur, and tendon lesions were rare. Obesity and hypertension of marked degree were not present. The radiological appearances were those of osteo-arthritis, the spinal changes being in the articular facets and spinous processes, while the disks were relatively normal. A controlled therapeutic trial in a small number of cases had not affected the arthritis, but the disease did not normally result in crippling.

(3) Biochemical Abnormalities in Rheumatism,* by PROFESSOR N. F. MACLAGAN (*London*).

The nature of the biochemical changes seen in patients with rheumatic diseases was discussed. While the advent of ACTH and cortisone had led to much interesting work on the biochemistry of patients treated with these drugs, it appeared to have reduced the interest in changes in untreated patients; these were nevertheless of fundamental interest. A brief review of the changes previously described in the serum proteins, flocculation tests, steroid excretion, and liver function, showed that most of the previous work had failed to differentiate between rheumatoid arthritis and ankylosing spondylitis.

The results were then given of studies on the serum proteins and of flocculation tests on patients at Westminster Hospital under the care of Dr. Dudley Hart. These were analysed with particular reference to the difference between rheumatoid arthritis and ankylosing spondylitis. Although the serum globulin results were

* This paper will appear in full in this Journal in June, 1952.

* Full details of this work will be published later.

practically identical in the two diseases, the serum albumin was markedly lower in rheumatoid arthritis while fibrinogen was higher in spondylitis. Among the flocculation tests, the ammonium sulphate and zinc sulphate tests failed to distinguish between the two diseases, but the gold and thymol tests were much more frequently positive in rheumatoid arthritis than in spondylitis.

These results supported clinical impressions as to the essential difference between the two conditions.

(4) Difficulties in the Assay of ACTH Potency, by DR. E. G. L. BYWATERS (*Taplow and London*), and DR. BARBARA ANSELL. (Read by Dr. Ansell.)

Differences between batches of pituitary corticotrophin found by various animal assay methods are not always congruent and may not be entirely relevant to anti-rheumatic potency. It was thought desirable to check the potency of various corticotrophin batches judging primarily by their clinical effects, and the results according to various methods of testing are presented. Seven different batches were tested on each of seven cases. It was found that the intramuscular route was not quite as informative as the intravenous one, although thrombosis of veins was troublesome with the latter. Furthermore some patients might become resistant, and in others symptoms might disappear; it was important, therefore, to retest the initial batch at the end of the testing period. It was better in general to separate periods of treatment by periods without treatment, and the optimum length of both of these periods was discussed. The dosage should be small enough not to mask minor differences in potency.

The criteria of hormone action used were the clinical yardsticks of joint range, pain, walking time, strength, temperature, etc. Eosinophil counts and 17-ketosteroid estimations were of little value. Despite these various difficulties it was possible to classify the seven batches tested into three categories: good, fairly good, and poor.

(5) Need for Caution in the Interpretation of Serial Tissue Biopsies,* by DR. BRUCE CRUICKSHANK (*Edinburgh*).

The President expressed the gratitude of the Society to the authors of these valuable papers, which had been presented most concisely with due regard to the rules of presentation.

After Friday's session Members adjourned to the Royal College of Physicians for the Annual Dinner.

After the Annual General Meeting on December 8, the President, Professor Sir Henry Cohen, being in the Chair, a Symposium on ACTH and Cortisone was given, and the following short papers were read:

* This paper will appear in full in this Journal in June, 1952.

(1) Effect of Cortisone on the Healing Process in the Eye, by DR. NORMAN ASHTON (*London*).

The value of the eye was demonstrated as an experimental organ in the investigation of the properties of cortisone. Experiments designed to study the effect of cortisone in small and large doses upon the healing of perforating wounds of the rabbit cornea were described, and it was shown that cortisone was able to modify the healing of the wounds by inhibiting the formation of the fibrinous coagulum, cellular infiltration, fibroblastic repair, and endothelial regeneration. The effect was related to the quantity of cortisone administered, being moderate with small doses and severe with large doses.

It has been reported by a number of experimental workers that cortisone exerted an inhibitory influence on the formation of new vessels during the process of inflammation and repair. This effect was well demonstrated in the cornea. Whether the vascularization was stimulated by burns or by the intracameral injection of alloxan, a method described by Ashton, Cook, and Langham (1951),* it could be modified although not completely arrested by cortisone, and this effect could be achieved more efficiently by subconjunctival than by systemic injection.

There was ample evidence that cortisone blocked the inflammatory reaction and this effect was as evident in the eye as elsewhere in the body. Since increased permeability of the capillaries is an accompaniment of all inflammatory processes an enquiry into the effect of cortisone on the permeability of the normal and abnormal capillary wall was therefore of importance. The eye lent itself ideally to such a study, for the permeability of the capillary walls could be assessed with considerable accuracy by the optical measurement of the appearance of fluorescein in the aqueous humour in the anterior chamber, after that dye has been injected intravenously. The transfer of fluorescein across the blood-aqueous barrier was thus a measure of the permeability of the capillary walls. This method had been used by Cook and MacDonald (1951)† in normal and inflamed eyes, and they had found that while cortisone had no effect on the capillary permeability in the normal eye it reduced the increase of permeability associated with inflammation.

This action clearly played an important role in the modification of inflammatory and repair processes, for it would obviously act in the direction of inhibiting the exudative manifestations and cellular infiltration and interfere with the demand of fibroblastic and other reparative activities for increased nutritional supplies.

Dr. Ashton felt, however, that before the site of action of cortisone in inflammation and repair could be localized, attention must be turned away from the behaviour of the reacting tissue elements, such as capillary wall, macrophages, fibroblasts, etc., and directed towards the

* *Brit. J. Ophthal.* (1951), **35**, 718.
† *Brit. J. Ophthal.* (1951), **35**, 730.

effect of cortisone upon the factors which normally stimulate their activity. Since these stimuli were themselves imperfectly understood, much research work might be required before it was possible to point to the first link in the chain of events which led to the cortisone effect.

Discussion.—DR. J. J. R. DUTHIE said that he had been interested in the subject from the point of view of capillary permeability changes. He suggested that the action of cortisone had not necessarily been localized; it might be directed upon some mechanism which induced the changes observed, rather than acting directly.

DR. E. G. L. BYWATERS thought that some idea of the mechanism concerned might be gained by observing the time taken by cortisone to produce the changes and how long it took to pre-treat in order to get the ciliary permeability changes. Did the effect come about rapidly?

DR. W. S. C. COPEMAN asked how the amount given experimentally to the rabbit—he thought Dr. Ashton had mentioned 2·5 mg.—compared with the dosage given to the human being. He took it that it would have to be arranged on a dosage-bodyweight basis. Was the term "capillary fragility" interchangeable with "capillary permeability" as Dr. Ashton had seemed to suggest?

DR. ASHTON replied that the effect of cortisone was fairly rapid—a matter of a few hours—,but that the full effect would take some days. With regard to the relation of quantities used in the rabbit to those used therapeutically in man, he thought this should not be evaluated on a bodyweight basis. The quantity they gave was roughly related to the therapeutic doses used in man as calculated on the basis of eye size.

THE PRESIDENT asked whether Dr. Ashton had carried out any metabolic investigations on these rabbits.

DR. ASHTON replied that he had not done so.

THE PRESIDENT suggested that it might have been discovered that change through other mechanisms was responsible.

(2) Individual responsiveness to ACTH and Cortisone, by MR. J. H. KELLGREN (*Manchester*).

The eosinopenic response to single doses of ACTH and cortisone has been studied extensively in four normal male subjects. As judged by this test the responsiveness of the four subjects differed greatly.*

The response to single doses of 50 mg. cortisone by mouth and 25 mg. ACTH intramuscularly had been studied in fourteen patients with rheumatoid disease, using the degree of eosinopenia, and changes in grip and joint tenderness as a measure of response. Wide individual variations in responsiveness were observed. Five patients responded well to both ACTH and cortisone, four to cortisone only, one to ACTH only, and four to neither hormone.

Seventeen patients with rheumatoid diseases were given standard 3-day courses of ACTH—25 mg. 6-hourly, and cortisone 50 mg. 6-hourly with a 4-day interval between courses, the same batch of ACTH and cortisone being used throughout. Response was measured in terms of eosinopenia, alteration in grip, joint tenderness, range of joint movement, and overall function. Four patients responded fully to both hormones. Four patients responded partially to both hormones. Four patients responded either fully or partially to cortisone and not at all to ACTH. One patient responded fully to ACTH and only partially to cortisone. Four patients showed no significant response to either hormone in the dosage used.

On withdrawal of the hormones, most patients returned rapidly to their pre-treatment condition, but three remained improved for considerable periods after both hormones. Five patients showed a temporary deterioration so that their condition was worse than before treatment. In general, withdrawal deterioration followed absence of response.

Discussion.—DR. G. D. KERSLEY said that this work was interesting in that it brought out the absence of correlation of the eosinophile response and the clinical response. He had had two quite outstanding cases where there was a good eosinophile response but no clinical response to ACTH, though one reacted to cortisone.

PROFESSOR L. S. P. DAVIDSON spoke of similar difficulties in treating cases of haemolytic anaemia.

MR. KELLGREN said, in reply, that the question of responsiveness to either, or both, or neither, of these agents from a practical point of view was rather important. Although it was by no means certain that a single test dose was conclusive, if one had eosinophil and subjective and clinical response in the rheumatic diseases, one could get a rough idea of what the outcome of a prolonged course would be. If ACTH evoked no response to the test dose and cortisone some response, then the latter was the drug to use and *vice versa*. This was something very well worth considering when one was thinking of employing either of these substances in any case whatsoever.

(3) Cortisone and ACTH in the Treatment of Rheumatoid Arthritis, by DR. W. S. C. COPEMAN (*London*).

It was fairly generally agreed that rheumatoid arthritis presented the most clear-cut indications for such therapy at this stage. Cortisone and ACTH seemed to have "arrived" in a bigger way in rheumatology than in any other branch of medicine. He proposed to talk only on the results found personally in a comparatively small series of cases which his group had been following up for just under a year.

In assessing the effects of these drugs, it was essential that the patients must be co-operative, of stable personality, and good witnesses, as so much depended on their own account of their condition. Cases selected were those which seemed to be potentially reversible or sufficiently so to allow the patient to return to work. This last practical consideration was the most important one. He did not find the length of history of the lesion

* Kellgren, J. H., and Janus, O. (1951). *Brit. med. J.*, **2**, 1183.

was important; it was not necessarily the earliest case that gave the best results.

Of twenty cases, seventeen had got back to a comfortable life and all the men were at work. Several of the women had returned to full work, and others to light housework with occasional full work. In only one case had treatment been stopped on account of side-effects, and after an interval further treatment had been possible. Only minor side-effects were noted; moderate rounding of the face, not uncommonly abscesses at the site of injection, and occasional oedema on high doses.

Progress was judged by assessing spontaneous pain, joint tenderness, grip test, functional test, and subjective assessment. He had not aimed at completely suppressing all the signs of the disease and this was fully explained to the patients beforehand. The aim was to get them back to work on the minimum effective dose.

Discussion.—PROF. L. S. P. DAVIDSON asked how many patients Dr. Copeman had treated with cortisone over a period of 6 months.

PROFESSOR S. J. HARTFALL asked whether intercurrent disease was a problem in patients on prolonged cortisone therapy.

DR. COPEMAN replied that, as regards the length of treatment, one patient had had cortisone for 3 months, one for 4 months, two for 5 months, three for 6 months, two for 7 months, four for 8 months, and one for 10 months.

This last was a patient who had just died from cerebral haemorrhage. She had been at work the day before her death, and was found dead in bed next morning. He doubted whether that death could be attributed to cortisone.

He did not know about intercurrent diseases. It was hoped to study this question in the next period of investigation, but concerning diabetes, they had produced one case which had been reported by Dr. Bishop and Dr. Glyn in the Section of Endocrinology of the Royal Society of Medicine the previous week. He believed that this was the only case so far recorded of permanent diabetes.

(4) Cortisone and ACTH in the Treatment of Ankylosing Spondylitis, by DR. H. F. WEST (*Sheffield*).

It appeared to be generally assumed that cortisone and ACTH affected rheumatoid arthritis and ankylosing spondylitis alike. The treatment of both might be considered under the headings of stiffness, pain, and deformity. ACTH and cortisone rapidly abolished the stiffness and allowed correction of that part of the deformity due to the presence of inflammatory exudate and the existence of muscle spasm. The pain may be subdivided into:

(*i*) spontaneous and aggressive;
(*ii*) that appearing during non-weightbearing movement and
(*iii*) that occasioned by weightbearing (i.e. the forcible rubbing together of two eroded bone surfaces).

In both diseases (*i*) is relieved and (*iii*) little affected. The difference between the diseases is apparent when (*ii*) is studied. A stage must come in an ankylosing joint when callus bridges the gap. At this stage movement of the joint will be painful and no relief will be expected from ACTH or cortisone. This state of affairs has been seen recently in a girl with fulminating ankylosing spondylitis. One hip, which was more advanced than the other, remained very painful on attempted movement, while the other became pain free. Such a state of affairs is not seen in rheumatoid joints treated with ACTH or cortisone. Thus it may be necessary in some cases of ankylosing spondylitis to reduce the dose in order to facilitate bony union.

Reference was made to other patients with hip involvement in ankylosing spondylitis who had remained free (on continuous therapy) for periods up to 15 months.

Discussion.—PROFESSOR S. J. HARTFALL described one case satisfactorily treated with ACTH and cortisone.

MR. J. H. KELLGREN said that one of the most useful points about cortisone was the quieting effect which it had on certain pain mechanisms. He thought they ought to take into account a little more deeply the mechanism by which pain was produced, and he gave on the blackboard a demonstration of the factors involved.

DR. F. DUDLEY HART described six cases of ankylosing spondylitis treated with cortisone or ACTH. The response was usually satisfactory but wore off very rapidly, unlike the beneficial effect obtained by deep *x*-ray therapy.

(5) Cortisone and ACTH in the Treatment of Still's Disease, by DR. E. G. L. BYWATERS (*Taplow*).

Still's disease was essentially rheumatoid arthritis occurring in children: so-called "specific" features (rash, fever, cervical spondylitis, and pericarditis) were seen from time to time in adults. Out of 92 children treated in the last 3 years, 29 had been treated with cortisone or corticotrophin. Results were very similar to those in adults; the dosage was the same as in adults except for extremely small children. Even large dosage (up to 500 mg. a day) was followed by a relapse within a week or so of stopping treatment. Complications were few in cases treated for up to 6 weeks. Amyloid did not seem to be affected within this time period. These substances controlled the symptoms in most cases, but relapse always occurred within a short time of stopping treatment.

(6) Cortisone and ACTH in the Treatment of Gout, by DR. G. D. KERSLEY (*Bath*).

Little had been written on this subject since the early days when Wolfson and others showed that an acute attack of gout could be cured within a few hours by ACTH, but that there was usually a severe attack within 4 to 5 days of stopping this, unless colchicine was given in large doses. He had explained this by suggesting that the trigger factors of gout acted as stresses, producing

a low level of circulating corticoids, which in a susceptible person brought on an acute attack. Again, in the low corticoid phase following cessation of ACTH therapy, a severe attack followed. He had stated that there was a low 17-ketosteroid excretion in gout, which in view of the reverse of an androgen deficiency—its usual onset coinciding with the incidence of familial hyperuricaemia, in males after puberty, and in females after the menopause—suggested to him an abnormal androgen metabolism in gout.

There had been surprisingly little evidence so far to substantiate or refute this suggestion. Random observations made in the laboratory at Bath on nine men with gout, gave an average reading of 11·2 mg./24 hrs, and in two women 6·1 mg./24 hrs, as compared with 13·4 mg. for ten male rheumatoids and 10·7 for eight female rheumatoids.

It had been attempted to use the ACTH withdrawal attack as a test for gout, but even when combined with a ketogenic diet it was found to be unreliable.

Cortisone had also been used in the treatment of severe tophaceous gout. One extremely severe case, over the period of 10 years, had gradually lost toes and fingers because the tophi had become so large. He had discharging sinuses on fingers, elbow, and feet. At the end of 3 weeks' treatment with 100 mg. cortisone per day, the tophi were appreciably less tense, and slightly smaller, and the discharge had decreased, whereas, up till that time they had steadily but slowly increased. There was no appreciable effect on the plasma uric acid, but the sedimentation rate fell a little.

To summarize—the effects of ACTH and cortisone in gout do, to some extent, bear out Selye's theories. ACTH is of practical value in cutting short a severe attack of gout, and cortisone may be of use in the comparatively rare cases of " malignant " tophaceous gout.

(7) ACTH and Cortisone. Trends in the U.S.A.,* by DR. J. J. R. DUTHIE (*Edinburgh*).

Dr. Duthie said that he had been fortunate in being able to visit the U.S.A. for 3 months under the auspices of the World Health Organization. He had visited most of the main centres in the East, and Middle West. One of the main objects of his trip was to meet those clinicians who had gained experience in the therapeutic use of ACTH and cortisone on a long-term basis, and to ascertain their present views on the value of these hormones in the treatment of the chronic rheumatic diseases. As one would expect, a considerable divergence of opinion had been found and he proposed to confine himself to a brief review of the main trends.

Preparations.—Oral cortisone had largely replaced parenteral cortisone and ACTH in long-term administration for obvious reasons. Its action was more rapid, and divided doses gave a smoother effect, but the speed of absorption on an empty stomach may cause undue stimulation, jitteriness, and inability to concentrate, so it was best taken after food.

Dosage.—Many clinicians had abandoned the high initial loading doses used in the early days—300-200-100 mg.—not entirely because of the greater danger of side-effects, but because patients who had experienced complete suppression found it difficult to accept even a partial return of symptoms when the dose was cut to a safer level, especially when the initial euphoria was followed by mental depression. One disadvantage of oral cortisone in this type of case was that dosage was more difficult to control on an out-patient basis. In the U.S.A. it was possible to buy cortisone without prescription—at a price—and patients might supplement their official supply. The method currently adopted was to start with 50-75 mg. daily and to adjust the dose up or down as required during the first few weeks of treatment. Complete suppression of symptoms was not aimed at, and the dose was stabilized when a useful degree of relief had been attained. This method had the advantage that, when it became obvious that the maintenance dose was going to be too high for safety, the medicine could be stopped before any harm had been done. Requirements in the individual varied, and the disease not infrequently " broke through ". Such an event might be heralded by a rise in blood sedimentation rate or eosinophils—or it might happen without a clinical flare-up.

The concensus of opinion to date was that about one-third of patients started on cortisone could be fairly well controlled with a dose (50-75 mg.) which caused no serious side-effects. Further experience might lower this figure, as the incidence of undesirable effects tended to increase as time went on.

Side-Effects.—Side-effects of greater or lesser significance occurred in about 50 per cent. of cases. Some were serious, some not, but the persistence of even minor effects—acne, obesity, mild oedema, mental depression, headaches, dizziness, tachycardia, blurring of vision, disturbances of menstruation, nervousness, increase in hair growth, etc.—might so disturb the patient that he voluntarily requested the drug to be stopped.

More serious effects were the masking of signs of intercurrent infections or surgical emergencies (appendicitis, perforation of the gut), activation of latent tuberculosis, haemorrhages from the gut, appearance or activation of peptic ulcers, perforation of existing ulcer, fractures of the long bones, collapse of vertebral bodies, thrombo-phlebitis with embolic complications, major psychosis, and coronary infarction. Complications of this type were commoner amongst women, and in the older age groups.

If the hormone had to be withdrawn for any reason, relapse was the rule sooner or later, and usually sooner. Although it had recently been claimed that long remissions had followed the use of very high doses—500 mg. daily for 14-30 days—yet all patients had eventually

* See also *Brit. med. J.* (1952), **1**, 341.

relapsed, so that the risks of such a procedure were hardly justified.

Withdrawal Syndrome.—In a proportion of cases, very distressing symptoms appeared when cortisone was stopped—the post-cortisone withdrawal syndrome. These patients complained of profound weakness, exhaustion, anorexia, mental depression, and generalized aching pain and stiffness. Their symptoms, which were relieved by sleep or rest, made worse by movement, and not controlled by previously effective doses of analgesics, were not wholly due to adrenal suppression, for they persisted when tests showed the cortex to be normally active, but they might arise from a relative deficiency of adrenal steroids in tissues conditioned to an abnormally high level. This suggested that in a proportion of cases cortisone might become a drug of addiction. The combination of the withdrawal syndrome with relapse in the arthritis produce a very distressing state of affairs. A very rare, but perhaps significant, complication of cortisone withdrawal had been the appearance, in several cases of rheumatoid arthritis, of the signs and symptoms of disseminated lupus, or of peri-arteritis nodosa. Dr. Duthie had personally seen three patients in which this occurred—all rheumatoids of some years' standing.

Mode of Action.—Intensive research had not yet revealed the mode of action of the adrenal steroids, but it was now generally accepted that the anti-inflammatory effect was non-specific and could be dissociated from the known effects on the metabolism of carbohydrate, fat, and protein.

Present Position.—Experience during the last two years had led the majority of physicians to adopt a much more conservative attitude to the use of cortisone or ACTH as a long-term method of treatment. It was no longer regarded as a substitute, but rather as an ancillary to other methods of treatment. In most clinics, orthodox methods, including gold, splints, and physiotherapy, were tried for several months first. Only those cases who continued to run a downhill course were considered, and cortisone was only used to augment the effect of standard treatment.

Complete suppression of symptoms was no longer aimed at. Early cases where damage was minimal were preferred, but in severely crippled cases the drug might be used to facilitate the application of other methods—manipulation, surgical operation, and corrective exercises—in the hope that the gain might be consolidated and cortisone then withdrawn. Orthopaedic surgeons felt that its use in this way had been a valuable contribution to treatment. There was no evidence that cortisone altered favourably the natural course of the disease. It was even possible that the increased activity allowed by suppression of inflammation may, in the continued presence of the unknown tissue irritant, lead to an increase in joint damage. Radiological progression of the disease without return of symptoms had been noted in cases receiving cortisone. At least an increase in the secondary osteo-arthritic changes in the affected joints put to excessive use under cortisone cover must be anticipated. Long-term follow-up of those cases would be of the greatest interest and importance.

The combination of cortisone with other substances, such as gold, insulin, and testosterone, had not been very encouraging, although it had been reported that PABA enhanced the effect of cortisone and allowed a substantial lowering of the dose. Different methods of administration—interrupted courses, low maintenance with booster doses, combination with ACTH—had not been very helpful in lowering the incidence of side-effects or preventing relapse on withdrawal. Cortisone was now available in a form which could be given intravenously, and it had been hoped that more prolonged effects might follow administration by this route, but such had not proved to be the case. The therapeutic effect was good, but not sustained. Intravenous ACTH had proved to be an economical method of producing maximum adrenal stimulation, 20-50 mg. being given by slow drip over 8-12 hours. Here again, hopes that more prolonged remission of symptoms might follow had not been fulfilled.

Intra-Articular Cortisone.—Diminution of pain and swelling had followed the intra-articular injection of 25-50 mg. cortisone acetate. Unfortunately, repeated injections appeared to have an irritating effect and symptoms recurred. Compound F, now available in limited quantities in America, was well tolerated, and repeated injections could be given without untoward effects. The beneficial effect lasted for 4-5 days on an average, and this method of treatment might prove of real value, especially in patients crippled by pain and swelling in one or both knees. No systemic effects were produced, and a weekly injection had proved adequate in most cases.

ACTH had largely been replaced by oral cortisone in long-term treatment, although its use was probably more physiological, and there was much less danger of severe withdrawal symptoms. A reliable long-acting preparation had not yet become available, but Armours hoped to produce one soon. The development of abscesses at injection sites was one serious complication liable to occur in out-patients. Astwood in Boston had produced highly purified preparations, and 1 mg. given in three divided doses had been sufficient to maintain good control in cases of rheumatoid arthritis. Side-effects were the same, but salt and water retention might be more troublesome. Variation in the potency of commercial preparations had caused a good deal of trouble, in Great Britain as well as in America.

Conclusion.—Opinion in America regarding the value of these hormones in long-term treatment of the chronic rheumatic diseases could be summarized as follows: Some believed that the benefits were so much greater than those following all other forms of treatment that their

use was fully justified, even on out-patients with the minimum of laboratory control. At the other extreme were those who thought the risks of long-term administration so great in most patients that it should never be advised. The majority of clinicians thought long-term therapy might be justifiable, if combined with orthodox methods in patients running a progressive downhill course. Short-term administration for a specific purpose (to cover manipulation or operation or to facilitate correction of deformities by other methods) was considered of real value. Intra-articular injection had only had a limited trial, but justified further study. The first enthusiasm had been replaced by a more cautious and conservative attitude. A tremendous amount of research into the hormones' mode of action was going on, but so far with little success. It was to be hoped that the experience gained in America would be fully utilized in planning therapeutic trials and research in Great Britain when cortisone and ACTH became cheaper and more plentiful, as they undoubtedly would in the not too distant future.

The President, in closing, said he did not intend to summarize what had been, in effect, a summary of the different aspects of ACTH and cortisone in the treatment of rheumatic disease. He had only to say how very much indebted the Society was to those who had made such admirable contributions. Much original work had been presented that morning and they looked forward with great interest to its completion.

For this instructive session with its experiences so freely related he expressed deep gratitude on behalf of the Executive.

SYMPOSIUM ON THE SUPRARENAL CORTEX COLSTON RESEARCH SOCIETY, UNIVERSITY OF BRISTOL

The fifth symposium arranged by the Colston Society will be held from March 31 to April 4, 1952, at the University of Bristol. The subject will be the Suprarenal Cortex, and the eighteen following papers will be presented:

1. **Preparation and Assay of ACTH,** by Dr. C. H. Li, *University of California, U.S.A.*
2. **Physical and Chemical Properties of ACTH,** by Professor F. G. Young, *Cambridge University.*
3. **Purification of ACTH,** by Dr. C. J. O. R. Morris, *The London Hospital, London.*
4. **Suprarenal Cortex. The Structural Background,** by Professor J. M. Yoffey, *University of Bristol.*
5. **Nature of Adrenal Cortical Secretion,** by Professor F. Verzar, *University of Basel, Switzerland.*
6. **Control of Secretory Activity of the Suprarenal Cortex, with special reference to the Isolated Preparation,** by Dr. Marthe Vogt, *University of Edinburgh.*
7. **Suprarenal Cortex and the Gonads,** by Professor S. Zuckerman, *University of Birmingham.*
8. **Metabolism of Adreno-Cortical Steroids,** by Professor G. F. Marrian, *University of Edinburgh.*
9. **Role of the Adrenal Glands in Infection and Intoxication,** by Dr. Harry J. Robinson, *Merck Institute, Rahway, U.S.A.*
10. **Adrenal Steroids and Personality Disorders,** by Dr. Hudson Hoagland, *Worcester Foundation, Shrewsbury, Mass., U.S.A.*
11. **Changes in Suprarenal Cortex Function in Shock and Hormone Treatments,** by Dr. R. E. Hemphill, *Bristol Mental Hospital.*
12. **Suprarenal Cortex Activity in the Endocrine equilibrium of Humans,** by Dr. M. Reiss, *Bristol Mental Hospital.*
13. **ACTH, Steroid Hormones, and Tissue Changes,** by Professor G. R. Cameron, *University College Hospital Medical School, London.*
14. **Role of Adrenal Cortex in Homeostasis,** by Dr. Dwight J. Ingle, *Upjohn Company, Mich., U.S.A.*
15. **Influence of the Suprarenal Cortex on Mineral and Water Metabolism,** by Professor H. Heller, *University of Bristol.*
16. **Surgery of the Suprarenal Gland with especial reference to the Cortex,** by Mr. L. R. Broster, *Charing Cross Hospital, London.*
17. **Clinical Applications of ACTH and Steroid Hormones,** by Professor E. B. Astwood, *Tafts College Medical School, Boston, Mass., U.S.A.*
18. **Clinical Responses as illustrated by the Rheumatic Diseases,** by Dr. G. D. Kersley, *Royal National Hospital for Rheumatic Diseases, Bath.*

Requests for admission should be sent to Dr. E. J. Field, Department of Anatomy, University of Bristol, Bristol 8.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the three abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, ABSTRACTS OF WORLD SURGERY, OBSTETRICS AND GYNAECOLOGY, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism: Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous): Sciatica: Gout: Non-Articular Rheumatism: General Pathology: ACTH, Cortisone, and other Steroids: Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section " ACTH, Cortisone, and other Steroids ", includes abstracts and titles of articles dealing with steroid research, which although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

The Use of Phenylephrine to aid Auscultation of Early Rheumatic Diastolic Murmurs. BESTERMAN, E. M. M. (1951). *Brit. med. J.*, **2**, 205.

The difficulty in recognizing mitral diastolic murmurs in the presence of tachycardia is well known. In order to prolong diastole, " phenylephrine " hydrochloride was given in doses of 0·25 mg. intravenously in children. This drug raises the arterial pressure in 2 minutes, and the pressure returns to normal in 4 to 8 minutes. The pulse rate falls by 36 beats per minute on the average, and the slowing lasts for 3 to 4 minutes. During this phase murmurs are intensified, vanished murmurs may reappear, and murmurs hitherto undetected may be brought out.

Of 64 patients, one complained of occipital headache and one of substernal oppression after the injection. The others had no symptoms. Accentuation of murmurs might outlast the effects on pulse and arterial pressure and might possibly be related to changes in stroke volume or other haemodynamic consequence of the drug.

J. McMichael.

Treatment of Circulatory Insufficiency in Rheumatic Children. (Лечение недостатчпости кровообращепия при ревматиэме в детком воэрасте.) LEITES, B. G. (1951). *Pediatrija*, **1**, 11.

The treatment of 75 children suffering from rheumatic carditis is described. Digitalis and allied drugs were used, and were given in larger doses than is usually considered appropriate to the age of the patient. From 0·09 to 0·24 g. of digitalis leaf was given daily, if necessary per rectum in 15 ml. of 30 per cent. glucose solution. The dose was reduced to one-half, then one-third as the effect of the drug appeared, and treatment was continued for 7 to 14 days or even 1 to 2 months in severe cases. Strophanthus was usually given before treatment with digitalis, and the two drugs were never used together; 5 to 10 minims (0·3 to 0·6 ml.) of the tincture was given daily for 10 to 30 days. Adonis vernalis was also given in some cases. In severe cases where digitalis was not fully effective, hypertonic glucose was given intravenously (15 ml. of 40 per cent. solution) and the patient was placed on a milk diet before giving digitalis. The diet had a diuretic effect which appeared on the third day, and diuresis was also produced by giving " mercusal " in doses of 0·6 to 2·0 g. daily for 4 to 5 days. Severe cases were treated in the open air in summer and sometimes also in winter. Of the 75 patients, eighteen were in the acute stage of the first attack; myocarditis and endocarditis were present in all, and pericarditis in twelve cases. Ten died, four improved but relapsed later, and four were discharged well. Digitalis was often ineffective, and strophanthus was used instead. A further 26 patients were suffering from relapses; mitral insufficiency was present in all, and aortic insufficiency in eight. Here also strophanthus was often more effective than digitalis. Of these 26 patients, sixteen were discharged improved and six died.

The remaining 31 patients were suffering from relapses of lesser severity. The disease was in all cases of 7 to 9 years' standing, and valvular damage was more marked; there were twenty cases of mitral stenosis and thirteen of tricuspid insufficiency. A good effect was obtained with full doses of digitalis, and as much as 0·32 g. was given daily in exceptional circumstances. Ten patients died, eight were discharged improved but relapsed later, and improvement was permanent in the remaining thirteen.

D. J. Bauer.

Decline in Mortality in Acute Rheumatic Fever in New Haven, Connecticut, 1920-1948. QUINN, R. W., and QUINN, J. P. (1951). *New Engl. J. Med.*, **245**, 211. 2 figs, 10 refs.

Acute Rheumatic Fever Treated with Cortisone and ACTH. A Report on Fourteen Cases. SMITH, H. L., and BARNES, A. R. (1951). *Minn. med.*, **34**, 854 and 889.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Involvement of the Hips in Rheumatoid Arthritis in Adults. (L'atteinte des hanches dans la polyarthrite chronique évolutive de l'adulte.) FORESTIER, J., ARLET, J., and JACQUELINE, F. (1951). *Rev. Rhum.*, **18**, 304. 4 figs.

Involvement of the hip-joints in rheumatoid arthritis is not commonly seen, but the authors found the incidence to be at least 10 per cent. A study of forty such cases (32 women, eight men) at Aix-les-Bains suggested that

the disease, usually in a severe form, had at the time of investigation, been present for a minimum period of 5 years. Four stages are described in the evolution of rheumatoid arthritis of the joint beginning, radiologically, with narrowing of the upper and inner part of the intra-articular space and ending with deformity of the femoral head and acetabulum, with displacement of both in an upward and inward direction. Arrest may take place at any stage, with development of bony sclerosis; bony ankylosis apparently never occurs.

The importance of early recognition is stressed, and one physical sign which may help to distinguish the condition from osteo-arthritis is mentioned—flexion of the hip is limited at an early stage. *D. Preiskel.*

Combined Salicylate and *para*-Aminobenzoic Acid (Pabalate) in the Treatment of Rheumatoid Arthritis. HOLLANDER, J. L., and HARRIS, T. N. (1951). *Amer. J. med. Sci.*, **221**, 398. 16 refs.

The salicylates have been the drugs of choice in the treatment of rheumatic disease for more than 75 years, and various combinations have been tried. The synergistic action of *p*-aminobenzoic acid (PABA) and sodium salicylate was discovered in 1946; the blood level of the latter could be increased by from 2 to 5 times by adding an equal quantity of the former. The " spreading factor ", hyaluronidase, is supposed to be inhibited by salicylates; this is important because hyaluronic acid is present in abundance in all body tissues subject to rheumatic disease, and the beneficial action of salicylates is due, it has been suggested, to this inhibition. As free hyaluronidase cannot be demonstrated in the blood or synovial fluids of patients with rheumatic disease, the index used is the titre of anti-hyaluronidase in the serum. The authors chose 27 cases of active rheumatoid arthritis for their study, observing the effects of salicylates alone, salicylates with PABA, and PABA alone. The mere raising of the blood salicylate level in rheumatoid arthritis does not appear to give greater relief from pain. The authors also found that the antihyaluronidase and antistreptolysin titres and the erythrocyte sedimentation rate were not significantly affected. Clinically, therefore, the addition of PABA offers little advantage in the treatment of rheumatoid arthritis. *D. Preiskel.*

The Effects of Denervation of the Adrenal on Rheumatoid Arthritis. (Les effets de l'énervation surrénalienne sur le rhumatisme chronique progressif inflammatoire.) GRABER-DUVERNAY, J., HERBERT, J. J., GERBAY, F., PAILLOT, J., and BLANCH-TERRADAS, F. (1951). *J. Méd. Lyon*, **32**, 537. 49 refs.

Five patients suffering from a severe form of rheumatoid arthritis were subjected to the operation of denervation of the adrenal glands by section of the great splanchnic nerve. Ordinary therapeutic measures had proved ineffective in these patients. All five were cases of long duration, most of the joints being affected; two patients were bed-ridden and two could just walk with the aid of crutches.

In all patients there was clear remission in most of the affected joints within 4 days of the operation. Within 8 hours joint pain at rest had disappeared and sleep improved. Walking was resumed within 10 to 12 days. Improvement in joints with severe destructive lesions did not last more than 30 to 40 days; in joints without much bone destruction relief was more prolonged.

In assessing the biological effects of denervation, the authors make allowance for the " stress " effect on the adrenals of the operative trauma. After operation in four control cases hyperglycaemia was observed, but did not last more than a few hours. After the denervation operation hyperglycaemia persisted for some 3 days. An eosinopenia observed after the control operations was followed by rapid rise to normal before the third day. After the denervation operations eosinopenia persisted for 30 days or more. The authors conclude that denervation causes a hypersecretion of cortisone, perhaps due to cortical vasodilatation.

Two patients in whom joint pains had returned after operation were given injections of ACTH. No beneficial effect was observed; in fact, the less severely affected joints became more painful. On the other hand, cortisone in unusually small doses proved effective in relieving pain: after 75 mg., then 50 mg. daily, to a total of 1·25 g., amelioration persisted for more than a month; then 25 mg. daily proved an effective maintenance dose. *Kenneth Stone.*

[This paper has also been published under the title *Énervation surrénalienne et polyarthrite chronique évolutive* in *Rhumatologie*, 1951, **3**, No. 3, 100, and under the title *Les effets de l'énervation surrénalienne sur les polyarthrites chroniques évolutives* in *Revue du Rhumatisme*, 1951, **18**, No. 6, 310.]

Rheumatoid Scleral Nodules (Scleromalacia Perforans) treated with Cortisone. TALKOV, R. H., COLPOYS, F. L., DAVIS, R. K., PAPPER, S., and FEINBERG, R. (1951). *Arch. intern. Med.*, **87**, 897. 6 figs, 19 refs.

Scleral rheumatic nodules were observed to disappear gradually under cortisone therapy. Histological observations portrayed an involution characterized by a large number of vacuolated and giant cells. *S. J. H. Miller.*

Sulphur-Fever (Sulfosin) Therapy in Rheumatoid Arthritis. (Svovlfeber (Sulfosin) ved arthriter.) SCHROEDER, K. (1951). *Nord. Med.*, **46**, 1437. Bibl.

The author claims that the parenteral sulphur treatment introduced by him in 1927 for the treatment of syphilis and gonorrhoea has a favourable effect on non-specific rheumatic disorders of the joints, acting on the mesenchyme. " Neo-sulfosin " is a 0·5 per cent. solution of sublimed sulphur dissolved in almond-oil, containing an anaesthetic. It should be administered intragluteally in doses rising from 1 to 10 ml. These injections cause a rise in temperature in the course of 12 hours, but within 1 to 2 days the temperature returns to normal, when a second injection may be administered. A course consists of 6 to 10 injections and may be repeated after an interval of 2 weeks. When a patient's temperature was high a course of neo-sulfosin brought it down (paradoxical effect) and the pains in the joints were considerably reduced.

While the effect on heart-action, pulse-rate, respiration, and blood pressure of neo-sulfosin corresponds to the temporary increase of temperature, normal conditions are restored in ratio with its fall.

The increase in leucocytes is remarkable, 40,000 to 50,000 having been found; this phenomenon is characteristic for all biological immunization reactions. The

erythrocyte sedimentation rate rises considerably 1 to 1½ hours after injections and remains high during the following 3 to 4 weeks. The author, however, believes that the effect of sulphur treatment does not rest only on pyrexia and the biological phenomena connected with it, but with the effect due to sulphur being " a substance reacting chemically with avidity ". *E. S. Fountain.*

Still's Disease: Interim Report of a Case Treated with Cortisone. WALT, F., RAFTERY, J. D., and JOHNSON, P.A. (1951). *S. Afr. med. J.*, **25**, 541. 1 fig., 4 refs.

The authors describe, with some interesting observations, the treatment with cortisone of a single case of rheumatoid arthritis of the infantile or Still's-disease group.

The patient, a girl [presumably European] aged 8¾ years, had a history of rheumatic joint manifestations for 5 years, with occasional attacks of asthma following infantile eczema. She was confined to bed with much functional disability, fixation of the neck, contractures of the wrist, and subcutaneous nodules at the elbows. The tip of the spleen was palpable, but there was no enlargement of lymph nodes. Radiological examination correlated with the clinical diagnosis of Still's disease.

After a control observation period of 14 days, cortisone was given by intramuscular injection: 150 mg. on the first day, then 100 mg. for 2 days, followed by 50 mg. daily; on the 9th, 10th, and 11th days the dose was increased to 75 mg. daily. A typical satisfactory response occurred, although this was considered to be somewhat delayed. In addition to the usual reversal of the disease process, subcutaneous nodules disappeared and the spleen became impalpable. Improvement was maintained over a period of 2 months by 50 mg. 3 times a week, but not by 25 mg. 3 times a week. Apart from the development of " moon-face " no side-reactions were observed.

Despite maintenance therapy, two relapses occurred, in one of which pyrexia, enlargement of the heart, and pericarditis developed. This was completely relieved by increasing the dose to 100 mg. daily for 5 days together with the administration of salicylates. Numerous laboratory findings are recorded. The child was apprehensive and resistant to treatment, which caused pain, and consistently refused to take the drug by mouth because of its taste. The authors conclude that treatment produced temporary symptomatic relief without cure, and that the maintenance dose did not prevent relapses or the occurrence of pericarditis. *Harry Coke.*

Pregnenolone. Preliminary Report on Pregnenolone Acetate and Acetoxypregnenolone in Arthritis and Soft Tissue Rheumatism. RAWLS, W. B., and ANCONA, V. C. (1951). *N.Y. St. J. Med.*, **51**, 1167.

The authors, working in the New York Polyclinic Post-Graduate Medical School and Hospital, report the effects of pregnenolone acetate and acetoxypregnenolone on fifty patients suffering from various types of rheumatic disease. In six patients with advanced or moderately advanced rheumatoid arthritis, no beneficial effect was observed from administration of 300-400 mg. pregnenolone intramuscularly daily for 18-21 days. Thirty-six cases of bursitis affecting either the subacromial or olecranon bursa were treated with pregnenolone acetate 300 mg. daily. Of fifteen acute cases without calcification, twelve improved after a few daily injections, and three showed no improvement. Of eight acute cases with calcification, six improved after a few injections, and two were unaffected. A few cases of osteo-arthritis were improved by pregnenolone therapy and the authors consider this improvement to be due to an effect on associated soft tissue lesions. The chief disadvantage of intramuscular pregnenolone therapy was local pain at the injection site. Two patients developed sterile abscesses. The authors conclude that pregnenolone therapy was beneficial in certain cases of soft tissue rheumatism.

[Unfortunately the authors do not describe any control cases, and it is in consequence difficult to decide to what extent the good results are due to pregnenolone therapy.] *B. E. W. Mace.*

Diagnosis of Rheumatoid Arthritis. Experience in 200 Cases. (Diagnostico de la artritis reumatoide. Experiencia en 200 casos.) LOSADA L., M., and FRANCE S., O. (1951). *Rev. med. Chile*, **79**, 439. Bibl.

Experiences in the Treatment of Rheumatoid Arthritis with Cortisone. DAVISON, S. (1951). *N.Y. St. J. Med.*, **51**, 2393. 16 refs.

Adrenal Cortex and Rheumatoid Arthritis. KENDALL, E. C. (1951). *Brit. med. J.*, **2**, 1295. 21 refs.

Remission in Rheumatoid Arthritis following Fever Therapy with Liver Damage. ARCHER, B. H. (1951). *N.Y. St. J. Med.*, **51**, 2657. 5 refs.

Still's Disease. (Maladie de Still.) LAMY, M. (1951). *Rev. Rhum.*, **18**, 345.

Treatment of Still's Disease with Cortisone and Gold. CHASE, J. D., and WILKINSON, J. M. (1951). *J. Mich. med. Soc.*, **50**, 1026 and 1066. 11 refs.

Medical Treatment of the Chauffard-Still Syndrome. (Traitement medical du syndrome de Chauffard-Still.) FRANÇON, F. (1951). *Rev. Rhum.*, **18**, 364.

Clinical Aspects of Chauffard's Syndrome in the Adult. (Aspects cliniques du syndrome de Chauffard chez l'adulte.) WEIL, M. P. (1951). *Rev. Rhum.*, **18**, 351.

Rheumatoid Arthritis and Occupation. [*In English.*] SNORRASON, E. (1951). *Acta med. scand.*, **140**, 355. 12 refs.

Cortisone in Rheumatoid Arthritis. An Interval Report. PRICE, A. E., LIGHTBODY, J. J., REVENO, W. S., and HEIDE, E. C. V. (1951). *J. Mich. med. Soc.*, **50**, 1015. 1 ref.

Splenectomy as a Method of Treatment in a Case of Felty's Syndrome. WILSON, W. H., and HAMILTON, A. T. (1951). *Sth. med. J. Bgham. Ala.*, **44**, 902. 2 figs, 4 refs.

Treatment of Rheumatoid Arthritis with *X* Rays. (Léčení deformativnich arthritid a arthros roentgenem.) FELLER, A. (1951). *Lék. Listy*, **6**, 582. 1 fig., 30 refs.

Problem of the Ulnar Deviation of the Fingers in Rheumatoid Arthritis. [*In English.*] SNORRASON, E. (1951). *Acta med. scand.*, **140**, 359. 3 figs, 34 refs.

Combined Use of Cortisone, ACTH, and Rehabilitation Techniques in Certain Arthritis Problems. Coss, J. A., and Ragan, C. A. (1951). *Arch. phys. Med.*, **32**, 572. 6 refs.

Psychological Factors in the Rheumatoid Type of Arthritis. (Influence psychique sur l'arthrite à type rhumatoïde.) Morin, E., and Rousseau, J. (1951). *Laval méd.*, **16**, 721. 5 figs.

Fifteen Years of Chrysotherapy in Rheumatoid Arthritis. (Quinze ans de chrysothérapie dans le rhumatisme articulaire chronique.) Simonart, E. F. (1951). *Rev. méd. Louvain*, **18**, 282.

Aetiology of Chronic Polyarthritis in Childhood. (L'étiologie des polyarthrites chroniques de l'enfance.) Wissler, H. (1951). *Rev. Rhum.*, **18**, 341.

Serum Complement in Rheumatoid Arthritis. Vaughan, J. H., Bayles, T. B., and Favour, C. B. (1951). *Amer. J. med. Sci.*, **222**, 186. 5 figs, 16 refs.

Clinical Evaluation of Aurothioglycolanilide (Lauron-endo) in Rheumatoid Arthritis. Merliss, R. R., Axelrod, B., Fineberg, J., and Melnik, M. (1951). *Ann. intern. Med.*, **35**, 352. 4 refs.

(Osteo-Arthritis)

A Series of 250 Cases of Cup Arthroplasty of the Hip. Early Results. (250 arthroplasties de la hanche avec interposition inerte. Premiers résultats.) d'Aubigné, R. M., Cauchoix, J., Ramadier, —., and Postel, — (1951). *Mém. Acad. Chir., Paris*, **77**, 199. 8 figs.

The authors have employed three types of operation in their series of 236 cases of cup arthroplasty of the hip:

(1) the Smith Petersen operation in cases in which the acetabular lesion was severe, but head and neck of the femur could be sufficiently preserved;

(2) Judet's operation in cases with a healthy acetabulum and defective head;

(3) acrylic arthroplasty, a combination of the two previous methods, in cases in which both the acetabulum and femoral head were diseased.

Early muscular re-éducation was practised post-operatively. Continuous traction through the tibial tuberosity in abduction was maintained for 15 days. The patients were got up at the end of a month. Weight-bearing, where the acetabulum had been reamed out, was not permitted for 4 to 5 months.

The operation has been used in the following groups of cases: (1) post-traumatic, 54; (2) arthritis of the hip with reaming of the acetabulum, 25; without reaming, 62; (3) congenital subluxation, 60; (4) congenital dislocation, 23; (5) old infection of the hip, 12. Of this total of 236 separate arthroplasties, 133 were reviewed.

Shock was avoided by good surgical and anaesthetic technique. Thrombosis was the worst risk encountered, and occurred in 25 cases with two deaths. There were nine cases of superficial post-operative infection and three of severe infection demanding removal of the prosthesis. There were 22 post-operative dislocations. In five cases there was excessive new bone formation around the hip and in two this was removed with success. In two cases fracture of the prosthesis occurred and it was replaced.

Results were assessed on a points system based on pre- and post-operative examination, and graded from 1 to 6 for pain, mobility, and gait. The results were the most satisfactory and most constant in fractures of the femoral neck. Necrosis of the head with a good neck and healthy hip seen at an early stage gave uniformly good results after Judet's operation.

After cup arthroplasty in cases of arthritis of the hip, two-thirds of the patients were almost free from pain and could flex the hip sufficiently to put on shoes and walk reasonably well. Only a third of the patients required a stick. After acrylic arthroplasty the results in four-fifths of the cases were similar to those in cup arthroplasty. There was slightly more improvement in mobility than with cup arthroplasty, although the improvement in gait was much the same. The functional result was not influenced as much as one would have thought by the pre-operative condition. Only in cases of severe disability in walking did arthroplasty provide amelioration. Preventive and early arthroplasty are therefore not advised.

In infective arthritis of the hip the results were satisfactory where infection had not recurred; there was a grave risk of lighting up an old infection, and the operation should be limited to bilateral cases or those with severe deformity.

In congenital dislocation of the hip the results were most encouraging and are to be reviewed in a subsequent paper. *J. G. Bonnin.*

Generalized Hypertrophic Osteoarthropathy. A Pathologic Study of Seven Cases. Gall, E. A., Bennett, G. A., and Bauer, W. (1951). *Amer. J. Path.*, **27**, 349. 22 figs, 32 refs.

Skeletal changes were examined in seven patients with generalized hypertrophic osteo-arthropathy, six having severe pulmonary disease and the seventh congenital heart disease. Subperiosteal new bone formation occurred in the long bones, beginning in the distal third of the bones of the forearm and leg. Joints showed chronic inflammatory changes in the synovia associated with degenerative changes in the articular cartilage. Clubbing of the digits was caused by soft-tissue changes, the predominant features being hyperaemia, oedema, increased amounts of loose-textured connective tissue, and mild chronic inflammation.

Theories of the aetiology of the condition are discussed, but no new views are advanced. *R. H. Heptinstall.*

(Spondylitis)

The Importance of Radiotherapy in the Treatment of Ankylosing Spondylitis. Richmond, J. J. (1951). *Proc. R. Soc. Med.*, **44**, 443. 4 figs.

A review is given of 160 cases of ankylosing spondylitis treated by the author over a period of 7 years. The technique involved irradiation of the sacro-iliac joints and whole spine, irrespective of the stage of the disease. A skin dose of 2,000r in 4 weeks was given to each section with x rays at 250 kV, 1 mm. Cu and 1 mm. Al filtration (H.V.L. 1·9 mm. Cu). This technique led to immediate symptomatic improvement of varying degree in 96 per cent. of cases and to freedom from recurrence of

symptoms in 80 per cent. [The latter figure includes cases treated 1 or more years previously, and cannot be regarded as a long-term result.] In the case of pre-menopausal females a tangential-field technique was used to minimize the *x*-ray dose to the ovaries. Although amenorrhoea may not result in these cases, the danger of unfavourable genetic changes in later generations as a result of irradiation received cannot be ignored. Radiation reactions during treatment included mild nausea and lethargy in most cases.

The erythrocyte sedimentation rates determined before and after treatment showed no significant difference.

Basil A. Stoll.

Pelvic and Extrapelvic Osteopathy in Rheumatoid Spondylitis. A Clinical and Roentgenographic Study of Ninety Cases. GUEST, C. M., and JACOBSON, H. G. (1951). *Amer. J. Roentgenol.*, **65**, 760. 8 figs, 11 refs.

After reviewing the literature the authors discuss the results of clinical and radiological examination in ninety cases of well-marked rheumatoid spondylitis.

Radiological changes consisted of irregular lytic defects with a punched-out appearance, irregular zones of increased bone density, and " whiskering " or " fringing " of the periphery of the bone. Clinically, there was sometimes pain and frequently tenderness over the site. Changes in the pelvic bones occurred in 74·4 per cent. of cases. The severity of the lesions corresponded to the extent of the spondylitis as a rule, but it was an early feature of the disease in a minority of cases. The commonest site was the ischial tuberosity, but the pubic symphyses and iliac crests were also often involved. Extrapelvic osteopathy occurred in eighteen of ninety cases, the sites being the femur, humeral head, acromion, carpal bones, sternal notch, angles of the scapulae, elbow, lower ends of the tibia and fibula, toes, and a patella. In 22·2 per cent. of cases there was no demonstrable pelvic or extrapelvic osteopathy, despite characteristic sacro-iliac and apophyseal joint changes.

It is concluded that the radiological changes are similar to those found in rheumatoid arthritis and the evidence suggests inflammatory rather than adaptive change.

Kathleen M. Lawther.

Iritis Associating with Spondylitis Ankylopoietica. CHAN, E., and SUN, S. F. (1951). *Chin. med. J.*, **69**, 147. 5 refs.

This is a report of one Chinese patient who attended hospital at the age of 26 with iritis of the left eye. This was his eighth attack, the first having occurred when he was 9 years old. From the age of 16, he had had intermittent pain in the right shoulder and knee, and when he was 20 years old, the spine became very painful and then bent forward; 2 years later the hips became ankylosed and there was no further pain. His mother suffered from " rheumatism ".

He had a gross kyphoscoliosis and ankylosis of both hip joints, and radiographic examination confirmed the diagnosis of ankylosing spondylitis. Examination of the left eye showed marked ciliary congestion and haziness of the cornea, without definite keratic precipitation. Under treatment the eye rapidly recovered.

The authors point out the similarity of the blood-aqueous barrier of the ciliary body to the blood-synovial fluid barrier in the synovial membrane. They suggest that iritis may be a pointing sign in ankylosing spondylitis, and that this association may occur more frequently than has been realized.

B. E. W. Mace.

Clinical Types of Chronic Progressive Ankylosing Spondylitis. (Formes cliniques de la spondylarthrite chronique progressive ankylosante.) WEISSENBACH, R. J., and FRANÇON, F. (1951). *Rev. argent. Reum.*, **16**, 58.

Rheumatoid (Ankylosing) Spondylitis: Its Early Manifestations and Early Diagnosis. YOUNG, J. H. (1951). *Med. J. Aust.*, **2**, 761. 5 refs.

A Contribution to the Diagnosis of Ankylosing Spondylitis. (Beitrag zur Diagnose des Morbus Bechterew.) HIMSTEDT, R. (1951). *Z. Rheumaforsch.*, **10**, 280. 8 refs.

(Miscellaneous)

A Five-Year Summary of X-Ray Therapy of Arthritis, Bursitis, and Radiculitis. GELBER, L. J. (1951). *Int. Rec. Med.*, **164**, 62. 29 refs.

The author reports his experience in the *x*-ray treatment of over 900 cases of arthritis, bursitis, and radiculitis in the course of the last 5 years. His results were encouraging, complete permanent relief from pain being obtained in many cases, while in the majority of the remainder there was long-lasting improvement. In this paper he analyses the results in 282 of these cases. He first stresses the social importance of rheumatic conditions, which affect 5 per cent. of the population of the United States, and cites a statement from the U.S. Government survey published in 1936 to the effect that " rheumatism ranks first in prevalence, second in causing chronic disability, second in causing invalidity (permanent disablement), and only fourteenth in causing death ". He then reviews the treatment of these conditions by cortisone, ACTH, and pregnenolone, and points to the disadvantages of these preparations. They often have only a temporary effect, and their administration may lead to physiological or psychical disturbances. He briefly touches on gold therapy, and mentions the difficulty of distinguishing the border-line between the therapeutic and the toxic dose.

The radiotherapy of arthritis was first introduced by Sokolov in 1897; although it was not much used in the U.S.A. until 1933, it was extensively employed in Europe. The author quotes the good results obtained with *x* rays by other workers in cases of spondylitis, especially those of Marie-Strümpell type. He considers early treatment to be essential, and states that the best results were obtained when radiotherapy was combined with breathing and postural exercises. The strength of the current was varied according to the size of the joint to be irradiated, a medium voltage being used for small joints and a high voltage for larger ones. In the acute stage three treatments a week for 2 to 3 weeks were given, followed by one treatment weekly for another 5 to 6 weeks. In chronic cases one or two treatments were given weekly for several weeks. The author found that arthritis of rheumatic origin required a higher voltage and heavier filtration than other conditions.

The most commonly occurring bursitis was that of the

subdeltoid bursa; bursitis affecting the olecranon or knee and prepatellar bursitis came next in frequency. The author mentions other conditions of the shoulder which may simulate bursitis, and warns that neglected bursitis may lead to "frozen shoulder". He also refers to brachial neuralgia and points out that this can easily be differentiated from bursitis because in the former, but not in the latter, neuralgia causes pain while the arm is at rest.

Radiotherapy should be continued until complete mobility of the joint is restored; this usually requires eight to ten sessions of 100r each at 180 kVp, with a filter of 0·5 mm. Cu and 1 mm. Al, and a focus-skin distance of 50 cm. Acute and subacute cases responded rapidly; in chronic cases a dose of 1,000r was often necessary to relieve pain and to restore mobility. Improvement was steady though slow.

The author discusses the aetiology of radiculitis, and concludes that this condition may be caused by any disease, toxic absorption, or mechanical factor which irritates the intraspinal or paraspinal elements. The main feature of radiculitis is pain of typical segmental distribution or arising in areas innervated by the affected nerve root. Involvement of a motor-nerve root results in muscular weakness, atrophy and electrical changes. In brachial-plexus radiculitis, which is often associated with bursitis and arthritis, the author recommends a dose of 1,200r. He also describes the dorsal-spine radiculitis syndrome. The possibility of the co-existence of radiculitis and coronary pain is pointed out. Segmental pain of the abdominal wall, the author states, may stimulate lesions of the gastro-intestinal or genito-urinary system.

In discussing sciatica the author considers only those cases which are due to arthritis. Radiotherapy in these cases proved to be most beneficial. He employed a high-voltage current with 0·5 mm. Cu and 1 mm. Al filtration, an average of 1,500r being given. A 6-inch cone was used to localize the irradiation. In the lumbo-sacral area great care should be exercised in both sexes and a dose of 600r never exceeded. The author considers that in these cases his results were satisfactory.

In giving *x*-ray treatment for rheumatic conditions great care must be taken of the skin, as it is hypersensitive over affected areas. Any reaction calls for curtailment or postponement of the treatment. A protective ointment containing antihistaminic factor was used with good results.

Seven interesting tables have been included, and these enable results to be appreciated at a glance.

L. G. Capra.

Arthritis due to Intestinal Amebiasis. RAPPAPORT, E. M., ROSSIEN, A. X., and ROSENBLUM, L. A. (1951). *Ann. intern. Med.*, **34**, 1224. 3 figs, 8 refs.

Four patients with recurrent polyarthritis of the rheumatoid type with spontaneous remissions and relapses were found to have intestinal amoebiasis which was causing only minor gastro-intestinal symptoms. Anti-amoebic therapy was accompanied by rapid disappearance of the arthritis, which did not recur subsequently.

The authors suggest that the arthritis in these cases was due to sensitization to *Entamoeba histolytica* or its by-products.

A. Gordon Beckett.

Anatomical and Radiological Examination of the Knee Joint. Arthrography. (Etude anatomique et radiologique du genou. Arthrographie.) VAN DE BERG, F., and CRÈVECOEUR, M. (1951). *J. belge Radiol.*, **34**, 7. 54 figs, bibl.

In this report from Liège of 100 arthrographs of the knee-joint, the anatomy of the normal joint, and the pathology of traumatic and degenerative lesions of the menisci, crossed ligaments, synovial cysts, and other pathological conditions, with their symptoms, are discussed at length.

While simple pneumoarthrography was often adequate, better results were obtained with a double-contrast method combining the injection of air and from 5 to 20 ml. of a 50 per cent. solution of "umbradil". The mixing of the injects was ensured by passive or active movements of the joint. The best position for photography was determined by screening, and it is claimed the pictures were clear and well defined. As umbradil may disappear in half an hour after injection, re-injection was sometimes necessary.

Apart from some intra-articular heat and one case of inflammation of the synovial sac, there were no untoward reactions. The number of cases examined was not considered sufficient to warrant any statistical conclusions. [There are 26 pages of reproductions of radiographs of the joint.]

Geo. Vilvandré.

Spondylolisthesis. HARRIS, R. I. (1951). *Ann. R. Coll. Surg. Engl.*, **8**, 259. 30 figs, 7 refs.

In a description of the pathological anatomy of spondylolistheses [the clearest yet published] the following are among the more important points mentioned. Most cases are bilateral and the fifth lumbar is the vertebra affected in 92 per cent. of cases (the fourth in 8 per cent.). The defect lies between the anterior fragment which consists of body, pedicles, transverse processes, and superior facets, and the posterior fragment consisting of laminae, spinous process, and inferior facets. The defect is filled with fibrous tissue. When the defect is present without forward slipping of the body the condition is called "spondylolysis" (symptomless and present in 5 per cent. of all spines), and when slipping occurs the condition is called "spondylolisthesis" (almost always associated with symptoms). Dislocation of the articular facets may occasionally be responsible for spondylolisthesis.

In discussing the causation of symptoms, the author states that trauma is often the final factor which determines the onset of symptoms, hyperextension being the commonest type of injury.

Clinically, pain and deformity are dependent upon, and roughly proportionate to, the amount of displacement. The pain experienced is of two types: lumbo-sacral pain, which is due to the instability, and root pain, due to involvement of the sacral plexus (occurring in 36 per cent. of cases).

The characteristic deformity includes:

(1) step-like break in alignment of the tips of the spines;

(2) rotation of the pelvis with an elevation of the anterior superior spine in relation to the posterior superior spine;

(3) shortening of the trunk, which is noticeable in severe cases;

(4) increased upper lumbar lordosis;

(5) folds in the loins.

Lateral radiographs demonstrate the lesion and the amount of slipping, but oblique views are valuable in demonstrating the defect.

Treatment is by fixation. Internal fixation by special grafting methods is indicated in the young, but for the older age group external fixation by spinal brace is preferable. Operative treatment is difficult and requires meticulous care in technique, more so than with spinal fusion for other causes. The fusion must be massive; fixation to the sacrum must be secure, as must also be the fixation to one body above the lesion. The technique must give immediate stability, and adequate post-operative protection is necessary for 4 months. Resumption of strenuous activity should be gradual. Two tibial grafts are countersunk into the sacrum and, if necessary, fixed with wire; they are firmly fixed above by wire sutures. These grafts are augmented by cancellous bone. The Stryker frame is used post-operatively. A method is described for correcting the displacement by skeletal traction through the femoral condyles and wings of the ilia. Of 67 patients treated by operation, 56 were cured of symptoms. The most frequent cause of an unsatisfactory result was failure to obtain bony fusion, and most failures were attributed to faulty operative technique. Persistence of severe deformity was responsible for a small group of failures. Thrombophlebitis occurred in five cases, none of which was fatal. Stress fracture of the tibia occurred frequently, but did not affect the final result.

[This Hunterian lecture is likely to become a classic. It is an excellent article in every way. The illustrations are good and the description of operative technique invaluable to the orthopaedic surgeon who has to deal with this troublesome condition.] *L. W. Plewes.*

The Conservative Treatment of Hernia of the Intervertebral Disk. (Die konservative Gipsbehandlung der Diskushernienischias.) BELART, W. (1951). *Z. Rheumaforsch.*, **10**, 12. 6 refs.

In the author's view the conservative treatment of prolapsed disk should be considered from the mechanical angle. By fixing the spine the swelling is diminished and it is possible for the prolapse to become replaced. If this does occur, then it forms a cicatrix during the rest period and leads to healing. In early and simple cases the only treatment that is necessary is a plaster of Paris bed. Generally this is used only in severe sciatica. The following criteria should be fulfilled:

(*a*) It is important that there should be rigidity of the lumbar spine with a scoliosis and a positive Lasègue. In most of these cases pain is aggravated on coughing and sneezing, and it is not usual to find any neurological signs, though these may occur.

(*b*) Simple lumbago may be the first manifestation of a prolapsed lumbar disk. After a certain period the pain diminishes by rest in bed with a board and mattress. No plaster is necessary in such cases. On the other hand, if the lumbago is complicated by sciatica with intense pain which has lasted for some time, then at the first consultation a plaster cast should be applied.

The back plaster should extend from the nape of the neck to the seat. A strong roll should be placed under the back while the plaster is put on, so as to produce a lordosis; this is essential in order to avoid pain. If 4 per cent. milk is added to the plaster of Paris it sets within 30 to 35 minutes. The patients should lie in the cast during day and night, although he may be allowed up for half-an-hour in the morning and evening. Patients become accustomed to this in about 2 days. Early cases are free from pain within 3 or 4 days, while old-standing sciatica might persist for a few weeks. Stiffness and a positive Lasègue sign persist after the pain has gone. The plaster of Paris cast should be removed only when the rigidity has gone, the Lasègue sign is negative, and sneezing and coughing cause no further pain. Mobilization is then the routine to follow, so that within 2 weeks movements are free and painless. The author has seen no recurrences.

The period required for cure is about 4 weeks; 6 weeks should suffice for nearly all cases. The latter period is necessary only if arthritis is also present. The only complications that the author has met with are pneumonia and infarction of the lung.

[This paper adds nothing new to present knowledge.] *Leon Gillis.*

Surgical Treatment of Herniated Lumbar Intervertebral Discs. Follow-up Study of 130 Patients without Spinal Fusion. ALFRED, K. S. (1951). *Amer. J. Surg.*, **81**, 390. 2 figs.

One hundred and thirty patients with prolapse of an intervertebral disk have been observed for 1 to 10 years after operation. Most of these patients had a long history of back pain and sciatica, the average duration of symptoms being over 3 years. In 59 of these patients myelographic studies were made pre-operatively, and in 53 the myelographic diagnosis was confirmed at the operation. Surgery was confined to exposure of the disk through a limited laminectomy; the bulging disk was identified, a cruciate incision made over the protrusion, the herniated material removed, and the disk space curetted: twelve patients required re-operation, in six of whom there was a recurrence at the original level and in one at a higher level. Two patients on re-exploration were found to have formed a cyst from injury to the dura, two had adhesions, and one extensive varices. At the follow-up examination, all patients, except one who was paralysed before the operation, has returned to work, 90 per cent. of them to their original jobs. About half of these on close questioning admitted the presence of occasional back or leg pain, but none felt the necessity for further treatment. Limitation of spinal movements was present in five patients. Return of reflexes after operation was uncommon, and many patients without pre-operative neurological abnormality showed absent ankle reflexes at re-examination. In this series only one patient, it was felt, might have benefited from spinal fusion. *Peter Ring.*

Herniations of the Cervical Intervertebral Disc and Scalenotomy. SHENKIN, H. A., and GROFF, R. A. (1951). *Surgery*, **29**, 540. 3 refs.

Four cases of intractable pain in the distribution of the brachial plexus are described where, on clinical and radiological evidence, a diagnosis was made of congestion of a posterior nerve root by a laterally placed cervical herniated nucleus pulposus. In one case the diagnosis was confirmed by myelography and in another both by myelography and exploratory laminectomy. Division

of the anterior scalenus muscle immediately relieved the pain in all four cases.

[This is an interesting and important paper.]

G. F. Rowbotham.

Application of the Technique of Radiological Enlargement to the Study of Chronic Joint Disease. (Application de la technique d'agrandissement radiologique à l'étude des affections articulaires chroniques.) PLAATS, G. J. VAN DER, and FONTAINE, J. (1951). *J. belge Radiol.*, **34**, 203. 10 figs.

By increasing the distance between the part of the body examined and the *x*-ray film it is possible to produce an enlarged radiographic image. Under certain technical conditions such an enlarged image may show minute anatomical changes which it would not have been possible to obtain by means of the ordinary radiographic technique. One of the most important conditions for the success of the method is the use of a rotating anode tube with a focus not larger than 0·3 mm. [For details of the technique the reader is referred to a previous publication by van der Plaats, but no precise reference to the publication is given.] *A. Orley.*

Vertebral Retroposition (Reversed Spondylolisthesis). GILLESPIE, H. W. (1951). *Brit. J. Radiol.*, **34**, 193. 10 figs, 11 refs.

The author examined a series of 493 cases in which the presence of lumbosacral disk protrusion was confirmed. Of these, 15·6 per cent. showed true retroposition of L 5 over S 1; 35 of the patients with retroposition were examined in more detail. The average backward displacement ranged from 0·3 to 0·9 cm.; in 71·4 per cent. the body of L 5 was slightly larger than that of the 1st sacral segment. In the normal spine this inequality does not disturb the continuous curved outline of the posterior vertebral alignment and therefore does not account for retroposition. It was found that the retroposition was greater than this difference in size in 91·4 per cent. of the cases.

The question of a false retroposition being produced by faulty tube positioning was investigated, and it was concluded that the degree of retroposition could be exaggerated or reduced by this means, but not eliminated. Rotation obliquely may produce an apparent displacement. Flexion or extension did not appreciably affect the degree of displacement. In 85·7 per cent. of the cases antero-posterior facets were found (8·6 per cent. had the internal-external type and 5·7 per cent. were mixed), in 85·7 per cent. the intervertebral space was reduced.

The case of a boy aged 4 years is cited in favour of a congenital aetiology associated with an acute lumbo-sacral angle. The incidence of lumbo-sacral anomalies was not found to be greater in the retroposition series than in a control group. The author states that retroposition may occur with

(1) disk protrusion;

(2) disk degeneration in association with spinal arthritis;

(3) rheumatoid spondylitis;

(4) infection;

(5) trauma.

He does not regard it as a cause of backache, but a a radiological indication of disk changes.

John H. L. Conway-Hughes.

Osteochondrodystrophia Deformans (Morquio Brailsford Disease). FELDMAN, N., DAVENPORT, M. E. (1951). *Arch. Dis. Childh.*, **26**, 279. 11 figs, 10 refs.

Four cases of osteochondrodystrophia deformans (Morquio's disease) are described. Two of the cases are of pure African native stock, but the others are of mixed African and coloured stock. These appear to be the first reported cases occurring in persons not of pure European racial origin. Consanguinity of the parents is present in three cases. The blood chemistry investigations show no significant departure from normal. A close relationship exists between the many different varieties of dyschondroplasia.—[*Authors' summary.*]

Kast's Syndrome. (Sindrome di Kast.) CABITZA, A. (1951). *Chir. Organi Mov.*, **36**, 264. 6 figs, 13 refs.

To the dozen or so cases of Kast's syndrome on record the author adds another, in a woman aged 24 years. Both hands showed extensive chondromatous swellings from the age of 6 onwards. Somewhat later coxa vara and outward convex curves of the upper third of the femur were discovered, while multiple small angiomata developed in the umbilical scar. There is a good reproduction of a radiograph of a symmetrical deformity of tibia and fibula which differs from deformities seen in other systemic affections of the skeleton, but resembles the dyschondromatous picture fairly closely.

I. Michaelis.

Reiter's Syndrome: A Case responding favourably to Neoarsphenamine. (Sindrome de Reiter: Um caso com resposta favorável ao 914.) MOURA, A. DE (1951). *Rev. portug. Obstet. Ginec. Cir.*, **4**, 70. 18 refs.

Ocular Complications of Arthritis. VAIL, D. (1951). *Sth. med. J. Bgham., Ala.*, **44**, 317. 3 refs.

A discussion on the association of ocular and rheumatic disease. Cortisone is probably effective in both by blocking the inflammatory response of collagen tissue to noxious agents. *S. J. H. Miller.*

Reiter's Syndrome. MCLACHLAN, A. E. W. (1951). *Bristol med.-chir. J.*, **68**, 87. 10 refs.

A description of the syndrome with a case report.

S. J. H. Miller.

Gout

Blood Flow in Gout. BARNETT, A. J. (1951). *Brit. med. J.*, **1**, 734. 2 figs, 2 refs.

Peripheral blood flow was measured by venous occlusion plethysmography in the feet of a man with bilateral podagra and obliterative vascular disease of the legs. During an acute gouty attack the resting blood flow in one foot was increased to 5 ml. per 100 ml. of limb volume per minute (normal 0·5 to 2·0 ml.), and increased further after a reactive-hyperaemia test. After subsidence of the acute attack the resting flow fell to normal, but again showed a reactive-hyperaemia response. In the contralateral foot the resting blood flow was at the upper limit of normal both during and after a gouty attack; it was not increased after the arterial occlusion test. The obliterative arteritis was most severe in this limb.

The author argues that these observations support the theory of a vasomotor disturbance with local production of a powerful vasodilator as the basis of the acute gouty attack. *Ellis Dresner.*

The Production of Leukaemoid Changes by Injection of Colchicine in the White Mouse. (Die Erzeugung leukämoider Veränderungen durch Colchicin bei der weissen Maus.) WIDMANN, H. (1951). *Z. ges. exp. Med.*, **117**, 227. 5 figs, 15 refs.

Mice weighing from 20 to 32 g. were given subcutaneous injections of 12 μg. colchicine on 3 or 4 consecutive days. This dosage produced within a day or two a high leucocyte count (in some animals of more than 100,000 cells per c.mm.) without a preceding leucopenia. The blood picture showed a shift to the left, with some normoblasts in the myeloid series.

In the bone marrow there was a decrease in granulocytes, but no structural damage such as is seen after bigger doses of the drug. The liver showed interstitial cell infiltration with numerous granulocytes, and extensive parenchymatous degeneration and coagulation necrosis. *H. Lehmann.*

The Effect of Benemid (*p*-[di-N-propylsulfamyl]-benzoic Acid) on Uric Acid Metabolism in One Normal and One Gouty Subject. BISHOP, C., RAND, R., and TALBOTT, J. H. (1951). *J. clin. Invest.*, **30**, 889. 8 figs, 4 refs.

"Benemid" is a substance having effects on the kidney similar to carinamide. The two subjects investigated had an intravenous injection of 25 to 50 mg. of ^{15}N-labelled uric acid and excretion was followed by the isotope dilution method. After several days 2 g. of Benemid daily for 3 days and then more labelled uric acid was injected.

In the non-gouty subject the initial uric-acid pool was 964 mg. and the turnover rate 0·66 pool per day. After benemid therapy the pool size dropped to 466 mg. and the turnover rate rose to 2·4 pools per day. This result is consistent with the view that Benemid inhibits the re-absorption of uric acid. There was a fall in serum uric acid level and a rise in urinary excretion. Similarly, in the subject with gouty arthritis initial pool size was 2,205 mg. and turnover rate 0·48 pool per day. After Benemid the pool size fell to 1,622 mg. and the turnover rate rose to 1·0 pool per day. There was a marked fall in serum uric-acid level, and more uric acid was excreted than could be accounted for by the observed diminution in pool size. Benemid in both subjects was a potent uricosuric agent. It acts probably by blocking uric-acid reabsorption in the tubules. *C. L. Cope.*

Plasma Uric Acid in Aged and Young Persons. PRAETORIUS, E. (1951). *J. Gerontol.*, **6**, 135. 2 refs.

Non-Articular Rheumatism

Shoulder-Hand Syndrome following Myocardial Infarction. Treatment by Procaine Block of the Stellate Ganglion. SWAN, D. M., and MCGOWAN, J. M. (1951). *J. Amer. med. Ass.*, **146**, 774. 3 figs, 5 refs.

Reflex neurovascular dystrophy of the upper extremity may be due to many different causes. It has been reported as occurring in as many as 10 to 20 per cent. of cases of myocardial infarction. It is characterized by painful shoulder disability with stiffness, swelling, and pain in the fingers and hand. After 3 to 6 months there may be disappearance of shoulder pain and hand swelling, but stiffness and flexion deformity of the fingers increase and there may be atrophy of the hand muscles and subcutaneous tissues. Later, trophic changes in the hand are prominent, with contractures, osteoporosis, and subluxations. The technique of stellate-ganglion block is described in detail, and three cases are reported to illustrate the complete success of this form of treatment. *T. Semple.*

560 Cases of Sciatica treated by Operation since 1939. (560 sciatiques opérées depuis 1939.) SÈZE, S. DE, and DOUIN, J. (1951). *Acta physiother. rheum. belg.*, **6**, 105.

This is a report of 560 patients operated upon during the last 12 years for prolapse of an intervertebral disk. Except for the latest one hundred cases all the operations were carried out by 34 different neurosurgeons from Paris hospitals.

Until 1946 laminectomy was the method of choice, but since then the interlaminar approach, more recently with careful protection of the insertions of the deep back muscles, has been used. Results have improved for three main reasons: (1) better diagnosis; (2) improved operative method; (3) the greater continuous experience of one single surgeon. Additional bone-grafting is only rarely resorted to, while extradural cutting of a nerve root (L 5 or S 1) is favoured in certain cases. [Diagnostic appraisal, surgical procedure, selection of patients, and end-results do not seem to differ much from those of other statistics.]

From middle age onwards a disk which has for long caused lumbago may protrude into a joint, and this occurrence is indicated by the appearance of additional sciatic pain. In such cases the surgeon should warn the patient that he will lose only his sciatic pain but not his lumbago.

[This is a clearly written article, but a minor criticism is necessary: once more percentages are used for the statistical assessment of small numbers.] *L. Michaelis.*

Bornholm Disease. GEFFEN, T. (1951). *Brit. med. J.*, **1**, 1185. 10 refs.

Outbreaks of Bornholm disease have been described from time to time in this country since the publication by Pickles in 1933 of his original observations in Yorkshire. Findlay and Howard (*Brit. med. J.*, 1950, **1**, 1233) discussed the possible association between this disease and the Coxsackie group of viruses.

The present paper describes a group of six patients with a clinical history approximating to that of Bornholm disease. Of the first five cases the Coxsackie virus was isolated in one, while in the other four a rising agglutination titre was found. No such confirmation was obtained in the sixth case.

[In some previously reported cases of Bornholm disease certain similarities between the symptomatology of epidemic myalgia and poliomyelitis have been described. There is, of course, no reason, from an epidemiological point of view, why patients should not harbour both poliomyelitis and Coxsackie viruses at the same time, but it has been pointed out that their biological behaviour is surprisingly similar. This paper tends to confirm

previous observations to the effect that members of the Coxsackie group of viruses are repeatedly found where poliomyelitis is epidemic.] *W. S. C. Copeman.*

Coxsackie Virus, Epidemic Myalgia (Bornholm Disease), and Intercostal Neuralgia. (Virus de Coxsackie. Myalgie épidémique, ou maladie de Bornholm, et névralgie intercostale.) RONSE, L. (1951). *Pr. méd.*, **59**, 996. 12 refs.

The author reviews the history of the isolation of the Coxsackie viruses and their association with the virus of acute poliomyelitis. The evidence put forward by various workers in favour of the theory that epidemic myalgia is caused by one of these viruses is considered. In particular he reviews in some detail the work of Findlay in Great Britain on the detection of complement-fixing antibodies developing in accidental and experimental infections with Coxsackie virus No. 2 which caused symptoms suggestive of epidemic myalgia. The technique of the complement-fixation reaction is described.

The author has studied in great detail an outbreak of epidemic myalgia at Ypres, and has had the sera of 24 patients examined by Findlay for complement-fixing antibodies. It was found that the patients with acute symptoms gave a positive reaction, whereas the sera from patients with a milder form of the disease were negative. In the discussion he describes the various forms which the disease may take and lists the frequency of various symptoms in 81 cases. He finds that the cases tend to fall into two groups—those with the features of epidemic myalgia and those more suggestive of intercostal neuralgia. Some patients showed signs of meningeal involvement, such as a positive Kernig sign or increased reflexes. He points out that the disease may simulate other conditions, such as perforated ulcer, peritonitis, or even a myocardial infarct, but he considers diaphragmatic spasm an important sign. The pain is also usually made worse by breathing, laughing, and movements of the trunk. Muscle rigidity is segmental in distribution. The only pleural complications he has seen have been in old cases of tuberculosis.

With regard to treatment, antibiotics had no effect, but sulphanilamide appeared to be of some value, with barbiturates and bromides in severe cases.

R. F. Jennison.

Place of Fibrositis amongst the Rheumatic Diseases. (Il problema della fibrosite nel quadro delle malattie reumatiche.) LUCHERINI, T., and CECCHI, E. (1951). *R.C. Ist. sup. San.*, **14**, 287. 56 figs, bibl.

The authors have produced nodular changes in the soft tissues by injecting one group of guinea-pigs with heterologous serum (using normal horse serum) and injecting another group with deoxycortone acetate; they examined these nodules histologically. The histological changes in the group treated with deoxycortone acetate showed big alterations in the subcutaneous connective tissue in the form of oedema, marked congestion of blood vessels, small haemorrhagic extravasations, diffuse infiltration with eosinophilic cells of the type described by Selye as " great, round cells with small dense nucleus in the interior of the granulomatous area ". There were less marked changes in the muscular connective tissue and in the subcutaneous periarticular tissue showing oedema, congestion, haemorrhages, and foci of histiocytic conglomeration in perivasal regions. Oedema and vasal congestion of medium intensity were noted in the synovial membrane as well. The muscular tissue showed limited areas of oedema, areas of degeneration, and fibroblastic proliferation of nodular aspect. All tissues were infiltrated with eosinophilic elements.

In the guinea-pigs subjected to injections of horse serum most marked changes were seen in the skin often of necrotic-ulcerative type (Arthus phenomenon). This group showed the same characteristic eosinophilic infiltrations.

The histological examination of a subcutaneous nodule removed from a man suffering from fibrositis showed fibrous tissue richly vascularized and congested. The vasal walls were thickened and in their periphery there were agglomerated round cells with deeply-stained nuclei. The connective tissue was oedematous and was infiltrated with fibroblasts, a few scattered neutrophils, and many eosinophils. One subcutaneous nodule, removed from a child suffering from rheumatic carditis, showed connective-tissue proliferation with many fibroblasts and giant cells with many nuclei. There was swelling caused by coagulated plasma, often with fibrinoid necrosis. The oedema was most marked in the neighbourhood of blood vessels, which showed congestion and eosinophilic infiltration.

The authors stress the uniformity of the histological changes: vasal congestion, oedema of the collagen tissue, cellular infiltration chiefly with eosinophils and histiocytic proliferation with fibroblasts, focal distribution in the vicinity of the vessels, and the possibility of reproduction by sensitization.

Fibrositis is considered to be an atypical variety of rheumatoid arthritis and to belong to the group of collagen diseases. *J. Mester.*

Relapsing Panniculitis (Weber-Christian Disease). Review of Literature and Report of a Case including Treatment with Cortisone. SHUMAN, C. R. (1951). *Arch. intern. Med.*, **87**, 669. 2 figs, 47 refs.

General Pathology

The Mucopolysaccharides of the Ground Substance of Connective Tissue. MEYER, K., and RAPPORT, M. M. (1951). *Science*, **113**, 596. 22 refs.

The mucopolysaccharides of skin, heart valves, aorta, tendon, synovial fluid, and umbilical cord were extracted with 0·33 to 0·5 N NaOH at 0° C. The extracts were neutralized with acetic acid and the protein was removed by treatment with amyl alcohol-chloroform, adsorption on Lloyd's reagent, or zinc hydroxide. Glycogen was destroyed by digestion with amylase. The polysaccharides were precipitated from calcium-acetate-acetic-acid solution by alcohol at 0° C. Five mucopolysaccharides can be distinguished:

(1) hyaluronic acid, which is sulphate-free, has a specific rotation of $-70°$ to $-80°$, and is rapidly digested by testicular and pneumococcal hyaluronidase;

(2) chondroitin sulphate A, which is found only in hyaline cartilage, has a specific rotation of $-30°$, and is hydrolysed by testicular but not by pneumococcal hyaluronidase;

(3) chrondroitin sulphate B, which has the same

composition as A, but a specific rotation of $-50°$, and is resistant to both types of hyaluronidase;

(4) chrondroitin sulphate C, which has the same composition as A, but a specific rotation of $-20°$, and is hydrolysed more rapidly by testicular hyaluronidase;

(5) hyaluronidase, obtained only from the cornea, with a specific rotation of $-56°$, is hydrolysed by both types of hyaluronidase. Its amino sugar is D-glucosamine, in contrast to the chrondroitin sulphates, which contain D-galactosamine.

It is possible to divide tissues into various groups according to their mucopolysaccharide content. Thus vitreous humour, synovial fluid, and peritoneal fluid from a patient with mesothelioma contained only hyaluronic acid. No hyaluronic acid was found in heart valves, aorta, or (probably) tendon. Skin and umbilical cord contained hyaluronic acid together with only one sulphate ester. *R. Barer.*

Chemical Constituents of Skeletal Muscle from Normal Subjects and Patients with Rheumatic and Non-Rheumatic Diseases. BIEN, E. J., ZIFF, M., and BUNIM, J. J. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 649. 2 figs, 14 refs.

Samples of muscle from thirteen healthy adult males and 27 patients with rheumatoid arthritis, gout, tuberculous spondylitis, and other diseases, were analysed for total protein, non-protein nitrogen, collagen, myosin, adenosinetriphosphatase activity, and water, correlation being made with parallel histological study. Methods are fully detailed and results are given as mean values plus and minus standard deviation for each group. No fat extraction was done.

Of the normal subjects there were some who showed lymphocytic infiltration histologically and a significantly smaller amount of myosin. The myosin fraction was reduced in all categories of patients except those with degenerative joint disease. Collagen, surprisingly, showed little variation from the normal range. In the group in which there was greater atrophy histologically (increase in sacrolemmal nuclei and diminution of mean fibre diameter) the collagen fraction of the total protein was not significantly altered, although there was marked decrease in myosin. Adenosinetriphosphatase activity was decreased significantly in the group of 27 patients. *E. G. L. Bywaters.*

Synovial Sarcomata. TILLOTSON, J. F., MCDONALD, J. R., and JANES, J. M. (1951). *J. Bone Jt Surg.*, **33A**, 459. 9 figs, 34 refs.

A total of 194 cases of synovial sarcomata have been collected from the literature, and to these are added 22 cases from the Mayo Clinic. The tumour appears macroscopically as a greyish-pink mass, often showing definite synovial attachment at one point. The consistency varies; there are often firm areas interspersed with gelatinous and at times haemorrhagic patches. There may be small spaces filled with a stringy yellow fluid. Microscopically there are tissue spaces with a cuboidal or endothelial lining; cell tufts may be present, varying from the compact groups of oval or polygonal cells to villous projections into glandular spaces; there is a varying fibrosarcomatous groundwork.

The clinical history is often long, the tumour often being associated with a joint in a lower limb. Local excision is frequently followed by recurrence and finally by general metastasis. Only one patient of the Mayo Clinic series has survived more than 5 years after operation without recurrence or metastasis. *Peter Ring.*

The Effect of parenterally administered Adrenocortical Extract on the Intradermal Spreading Action of Hyaluronidase. HAYES, M. A., and BAKER, B. L. (1951). *Endocrinology*, **49**, 379. 2 figs, 13 refs.

Fatal Case of Still's Disease Complicated by Amyloidosis. ARMSTRONG, J. R. (1951). *Brit. med. J.*, **2**, 1261. 7 refs.

Laboratory Aids in Diagnosis and Treatment of Rheumatoid Arthritis. WELLS, B. B., ROSS, S. W., and LOWRY, R. D. (1951). *Tex. J. Med.*, **47**, 700. 19 refs.

Fibrinoid and Hydroxyproline of the Rheumatoid Subcutaneous Nodule. BIEN, E. J., and ZIFF, M. (1951). *Proc. Soc. exp. Biol., N.Y.*, **78**, 327. 8 refs.

Disturbances of Protein Metabolism in Rheumatoid Arthritis. (Les troubles du metabolisme protidique dans les polyarthrites.) GAUCHER, M. (1951). *Rev. Rhum.*, **18**, 417. 1 fig.

ACTH, Cortisone, and Other Steroids

Epilepsy in Systemic Lupus Erythematosus. Effect of Cortisone and ACTH. RUSSELL, P. W., HASERICK, J. R., and ZUCKER, E. M. (1951). *Arch. intern. Med.*, **88**, 78. 6 figs, 27 refs.

Previous work on the association of convulsions with lupus erythematosus has led to the view that the occurrence of epilepsy with rheumatoid arthritis may often indicate the existence of systemic lupus erythematosus. Convulsions were noted in 22 of 144 cases of lupus erythematosus described in the literature, the seizures being terminal in fifteen, and in seven of the authors' series of 28 consecutive patients with a positive reaction to the plasma L.E. test. In two of these seven the convulsions preceded the development of typical symptoms by 2 and 16 years respectively. In three further cases without convulsions there was evidence of cerebral dysrhythmia or histopathological changes. The frequency of convulsions bore some relation to disease activity, their occurrence in some cases being associated with exacerbation. Cortisone or ACTH diminished or abolished the convulsions in some cases; "dilantin" (phenytoinum sodium), which was given to five patients, was without effect.

Abnormal patterns in the electroencephalogram (EEG) were observed in seven of eleven consecutive patients with active lupus erythematosus, including all the five patients with convulsions and two of six in whom there were no convulsions or other cerebral manifestations. Two types of electrical change were noted, the common feature being a slow, diffuse delta activity unequal on the two sides, contrasting with the symmetrical slow, diffuse waves found in idiopathic convulsive conditions. The degree of EEG abnormality tended to fluctuate with the clinical state.

The histological changes seen in the brain varied considerably and none could be regarded as specific. *R. Crawford.*

Changes in the Bone Marrow in Rheumatoid Arthritis; Effect of Cortisone. (Ueber die Beteiligung des Knochenmarkes bei der Polyarthritis chronica rheumatica und ihre Beeinflussung durch Cortison.) JASIŃSKI, B., and STAECHELIN, A. (1951). *Schweiz. med. Wschr.*, **81**, 619. 13 refs.

During the last 10 years eighty patients with rheumatoid arthritis have been investigated, six of them having been treated by short courses of comparatively small doses of cortisone. Chronic granulocytopenia was present in five cases and in one of them an anaemia. Bone-marrow biopsy showed maturation arrest at the metamyelocyte and stab-cell stages; this was not influenced by cortisone. The functional activity of leucocytes was investigated by studying the disposal of bacterial substances, using a preparation made from *Bacterium coli*; this was diminished throughout. In five cases in which the leucopenia was not so severe and in five with anaemia, bone-marrow changes were similar. In another case thrombocytopenia persisted for 2 months. Of the four patients without changes in the blood count, two were given cortisone. In most cases the proportion of plasma cells in the marrow was less than 2 per cent., but in one it was 3·4 per cent. [This is much less than found by Hayhoe and Robertson Smith, *J. clin. Path.*, 1951, **4**, 47.] All the sixteen cases in which there was evidence of bone-marrow damage showed reactions to the injection of bacterial products similar to those seen in marrow hypoplasia or aplastic anaemia. *E. Neumark.*

Intravenously Administered ACTH. A Preliminary Report. RENOLD, A. E., FORSHAM, P. H., MAISTERRENA, J. and THORN, G. W. (1951). *New Engl. J. Med.*, **244**, 796. 7 refs.

The authors describe their experience with the intravenous administration of ACTH in 100 subjects. The investigation was carried out at the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School. ACTH was dissolved in 500 ml. saline solution or 5 per cent. dextrose solution and infused intravenously over a period of 8 hours. The fall in circulating eosinophils was regarded as a qualitative measure of adrenal response, and the rise in urinary 17-ketosteroids as a quantitative measure. It was found that an 8-hour intravenous administration of ACTH stimulated the adrenal cortex for 16 to 24 hours, thus approximately meeting the patient's requirements for the day. When 20 mg. ACTH was given daily to a subject with normal adrenal glands, a maximum response was attained in from 3 to 8 days. With the duration of infusion constant at 8 hours, adrenal cortical stimulation increased approximately linearly with the dose of ACTH to 10-20 mg. Larger doses did not appear to increase adrenal cortical activation any further once this maximum was reached. The effect of 20 mg. ACTH given intravenously over a period of 8 hours was comparable to that obtained by intramuscular injection of 5 to 10 times this dose when injected 6-hourly in 24 hours.

No anaphylactic reactions were noted in over 100 patients or normal subjects, many of whom had received repeated infusions. The authors advise, however, that until a larger group has been studied patients should be watched for the first 30 minutes of the infusion for any evidence of anaphylaxis. No evidence was found of a diminished response to ACTH with repeated administration. Intravenously administered ACTH resulted in a normal adrenal response in four patients who had become unresponsive to the same preparation of ACTH injected intramuscularly.

The authors describe cases of rheumatoid arthritis, psoriasis, and exfoliative dermatitis which illustrate the effectiveness of intravenously administered ACTH in one-fifth to one-tenth of the dosage usually required by the intramuscular route. *C. E. Quin.*

Sustained Pituitary Adrenocorticotropic Hormone (ACTH). PETERMAN, E. A. (1951). *J. Mich. med. Soc.*, **50**, 1010. 2 figs, 7 refs.

Twenty-four rheumatoid arthritis patients were given daily intramuscular injections of pituitary adrenocorticotropic hormone (ACTH) suspended in 5 ml. of a sustaining menstruum consisting of 18 per cent. nonantigenic gelatin made hypertonic with 8 per cent. dextrose. Serial circulating eosinophile counts showed maximum physiologic effect from a single injection to be reached in from 5 to 12 hours. The effect was well maintained from 12 to 24 hours, gradually diminishing from 24 to 48 hours. As each succeeding daily injection of the hormone was given before the effect of the preceding one was gone, a mild continuous adrenal cortical stimulation was obtained. Adequate clinical response was maintained with approximately 60 per cent. less hormone than was formerly used. Chronically ill patients, in whom pituitary adrenocorticotropic hormone was formerly thought to be contraindicated, responded satisfactorily to this treatment.—[*Author's summary.*]

A Comparative Study of Pregnenolone, 21-Acetoxypregnenolone and ACTH. BRUGSCH, H. G., and MANNING, R. A. (1951). *New Engl. J. Med.*, **244**, 628. 4 figs, 8 refs.

This is a study of 21 patients, of whom eighteen had severe chronic rheumatoid arthritis, two ankylosing spondylitis and one gout. Sixteen cases were given pregnenolone intramuscularly in doses of 100-300 mg. Nine of these patients were afterwards given ACTH.

Most of the patients given pregnenolone showed some decrease in discomfort at some stage, but there was no evidence of a sustained action of the drug. One patient felt much better after 2 months' treatment: she later had ACTH with much greater benefit, but relapsed after this was discontinued. With this exception, no patient given pregnenolone or 21-acetoxypregnenolone produced any noticeable improvement in joint function, gain in weight, or reduction in sedimentation rate.

When ACTH was given, rapid clinical recovery occurred during the course of treatment.

Side effects of pregnenolone administration were rare, and usually confined to painful lumps at the site of injection.

The authors have used ACTH as a standard against which the other remedies are measured. On their results, pregnenolone and 21-acetoxypregnenolone are innocuous but have no useful antirheumatic effect.

B. E. W. Mace.

Cortisone in the Treatment of Acute Rheumatic Fever. RATHBUN, J. C., MCALPINE, H., and MANNING, G. W. (1951). *Canad. Med. Ass. J.*, **65**, 113. 3 figs, 9 refs.

The authors report the effect of cortisone on an 8-year-old girl suffering from acute rheumatic fever. The patient had been ill for 17 days. She had been

treated with salicylates, but in spite of this her condition had deteriorated. On admission she was febrile, erythema marginatum was present and there were signs of cardiac failure. There was marked cardiac enlargement clinically and radiologically. An E.C.G. showed changes compatible with acute pericarditis. Blood examination revealed: Hb 63 per cent.; W.B.C. 21,300 per cu. mm.; E.S.R. 115 mm. in first hour.

She was treated with cortisone for 18 days. The temperature began to fall on the third day and was normal on the seventh day. At the same time signs of cardiac failure disappeared. A systolic murmur was present on admission and a mild diastolic murmur developed during cortisone therapy and persisted for three months. Auscultatory findings were confirmed by phonocardiograms. An *x* ray revealed a dramatic reduction in heart size to just slightly above normal on the seventh day. Electrocardiograms returned to normal more slowly. The erythrocyte sedimentation rate returned to normal on the fourteenth day.

One month after cessation of cortisone the patient was allowed up in a chair, but this caused a rise in temperature and erythrocyte sedimentation rate. In all, four months' bed rest was necessary before the patient was allowed up.

The authors consider that the rapid clearing of cardiac failure and return to normal cardiac size on the seventh day of treatment suggest that cortisone has a beneficial effect on the damaged myocardium. *C. E. Quin.*

Further Experiences with Prolonged Treatment of Rheumatoid Arthritis with ACTH and with Gold. GOSLINGS, J., HIJMANS, W., QUERIDO, A., and KASSENAAR, A. A. H. (1951). *Brit. med. J.*, **2**, 698. 5 figs, 12 refs.

In an earlier paper (*Brit. med. J.*, 1950, **2**, 1019) was described the treatment of rheumatoid arthritis with small doses of ACTH over a prolonged period. The authors now report further results, but deal mainly with the development of a " refractory state " to ACTH after some weeks' treatment. ACTH was given to twenty patients for periods of 1½ to 8 months; all of them showed initial improvement, but relapse in some degree occurred in nineteen either during or after treatment. It was observed that after a variable period of treatment the dose of ACTH which had originally been effective was no longer so, and clinical deterioration occurred.

Attempts were made to establish the cause of these relapses under treatment. It was found that in six patients who no longer responded to ACTH cortisone produced a satisfactory remission, and it is concluded from this that a diminished response to cortisone-like substances in the " target organs " is not the cause of the ACTH-refractory state. Tests of thyroid function with radio-active iodine gave normal results in four patients who had failed to respond to ACTH: this probably excludes " corticogenic hypothyroidism " as a cause of this unresponsiveness. The possibility that the adrenal glands fail to respond to ACTH after a time could not be dismissed, but this is considered unlikely: the level of 17-ketosteroid excretion and the degree of eosinopenia often bore no relation to the clinical picture. The intravenous administration of ascorbic acid in large doses in an attempt to restore the theoretically depleted adrenal cortical content was without effect.

Observations made with different batches and makes of ACTH suggest that after a prolonged period neutralizing antibodies may develop against particular batches of ACTH, and this is possibly the basis of the ACTH-refractory state. *B. E. W. Mace.*

Development of Active Pulmonary Tuberculosis during ACTH and Cortisone Therapy. FRED, L., LEVIN, M. H., RIVO, J. B., and BARRETT, T. F. (1951). *J. Amer. med. Ass.*, **147**, 242. 4 figs, 21 refs.

This is the case report of a 58-year-old man with rheumatoid arthritis and chronic hepatitis of 1½ years' duration who was given treatment with ACTH and later cortisone, during which he developed a pulmonary lesion that was eventually found to be tuberculous.

Before treatment was started the patient had a persistent pyrexia for which extensive investigations revealed no cause and which was presumed to be a manifestation of rheumatoid arthritis. A chest radiograph was clear. ACTH was effective in relieving the symptoms and the pyrexia, but after 6 weeks there was an increase in cough and a rise in temperature, and an inflammatory lesion in the right lung field was found on radiological examination. This lesion gradually extended, and 6 weeks later tubercle bacilli were found in the sputum. The patient survived, but has made little progress.

The development of tuberculosis in this patient may possibly have no connexion with the hormone therapy (just before treatment was started he was in the next bed to a tuberculous patient), although this is most likely. The authors point out the increasing evidence that ACTH and cortisone exert much influence on physiological reactions to insult, and suggest that until information is more precise these hormones should be used with extreme caution. *B. E. W. Mace.*

Subcutaneous Implantation of Cortisone Pellets in Rheumatoid Arthritis. HENDERSON, E., GRAY, J. W., WEINBERG, M., and MERRICK, E. Z. (1951). *Science*, **114**, 243. 9 refs.

Eight patients with rheumatoid arthritis of severe grade received subcutaneous implantations of 900 mg. cortisone in the form of twelve pellets, each of 75 mg. Prompt clinical improvement of moderate degree occurred in all patients and was sustained for 2 to 4 weeks, whereupon all except one relapsed to their pre-treatment condition. It is considered that subcutaneous implantation is a possible means of giving cortisone.
G. M. Findlay.

Experiences in the Treatment of Juvenile Rheumatoid Arthritis with ACTH. [In English.] VAN CREVELD, S., DINGEMANSE, E., HUIS IN'T VELD, L. G., and KUIPERS, F. (1951). *Ann. paediatr., Basel*, **172**, 201. 16 figs, 26 refs.

The authors record their experiences of the treatment of three cases of juvenile rheumatoid arthritis with ACTH. In all cases the clinical state was assessed and the following investigations were carried out: glucose tolerance test; serum potassium, chloride, and protein estimations; uric-acid-creatine ratio; 17-ketosteroid excretion; erythrocyte sedimentation rate (E.S.R.); and antihyaluronidase [type not stated] titres.

The first patient was a girl aged 13 with chronic rheumatoid arthritis. On 50 mg. ACTH per day there was clinical improvement. As the dose of ACTH was

lowered the E.S.R. rose, but the clinical improvement persisted. When ACTH was replaced by saline clinical relapse occurred. An exacerbation of arthritis, 5 months after ACTH had first been given, responded poorly to a fresh course of ACTH, but the authors still thought the patient's condition was much improved by the total ACTH course. A second patient, aged 4, improved on 4 mg. ACTH per day, but showed only a subjective improvement on a daily dose of 2 mg. Decreased sugar tolerance and pigmentation appeared as side-effects with the larger [though still very small] dose. A third patient also showed some improvement. The authors add an interesting study of 17-ketosteroid excretion.

[It is notoriously difficult to draw conclusions on the treatment of a disease like rheumatoid arthritis which is always liable to undergo spontaneous remissions, and the authors might have done well to let their judgment be tempered with more caution on this score. The statement that " one must conclude that in the pathogenesis of rheumatic diseases the adrenal cortex must play a part " seems unwarranted.] *G. Loewi.*

Spontaneous Hypoglycaemia after Insulin Therapy in Rheumatoid Arthritis. KERSLEY, G. D., MANDEL, L., TAYLOR, K. B., and JEFFREY, M. R. (1951). *Brit. med. J.*, **2**, 578. 1 fig, 2 refs.

The authors report two cases of spontaneous hypoglycaemia which occurred shortly after the cessation of insulin hypoglycaemic therapy which had been given to a series of patients with rheumatoid arthritis. The attacks were controlled by a high-protein diet with a feed at bedtime, and the tendency to them disappeared within 2 weeks. *W. S. C. Copeman.*

Hypoglycaemia in Treatment of Rheumatoid Arthritis. KERSLEY, G. D., MANDEL, L., JEFFREY, M. R., BENE, E., and TAYLOR, K. B. (1951). *Brit. med. J.*, **2**, 574. 1 fig, 5 refs.

In this paper is presented the further work which has been done by the authors in an endeavour to stimulate the pituitary-adrenal complex by means of hypoglycaemia. They report marked temporary improvement in 44 per cent. of 72 patients with rheumatoid arthritis who had been subjected to this procedure. Complete clinical remission was obtained in seven cases after 6 months. In a control series of patients on a simple hospital regimen and without hypoglycaemia, only 14 per cent. had marked improvement. A second course of treatment was less successful than the first.

The authors consider that the clinical response to hypoglycaemia can be correlated closely with that evoked by ACTH. *W. S. C. Copeman.*

Intravenous Use of Pituitary Adrenocorticotropic Hormone (ACTH). A Report on its Administration in Twenty-five Patients. MANDEL, W., SINGER, M. J., GUDMUNDSON, R., MEISTER, L., and MODERN, F. W. S. (1951). *J. Amer. med. Ass.*, **746**, 546. 11 refs.

The authors have given ACTH intravenously to 25 patients under treatment in the Veterans' Administration Hospital, Long Beach, California. ACTH was administered each day in one of three ways: by continuous intravenous infusion for 8 to 20 hours, by intermittent intravenous injection every 6 hours, and by continuous intramuscular drip. The daily dose for intravenous administration varied between 5 and 20 mg. and was dissolved in distilled water containing 5 per cent. glucose and 0·2 per cent. potassium chloride. When given for 20 hours, the ACTH was placed in 1 to 2 litres of fluid; when it was given for 8 to 12 hours, 0·5 to 1 litre was used. Of the 25 patients in this series, twelve had rheumatoid arthritis, three rheumatoid spondylitis, four bronchial asthma, and one lupus erythematosus, one polyarteritis nodosa, one scleroderma, one rheumatic fever, one neurodermatitis, and one eczematoid dermatitis.

It was found that all patients responded to intravenous administration of 5 to 10 mg. ACTH and many patients could be maintained on doses between 2·5 and 5 mg. daily.

The response to continuous infusion of a single dose was roughly proportional to duration of administration. Thus, in one patient given a constant daily dose of ACTH, the 20-hour infusion was more effective than the 12-hour infusion, and this in turn was more effective than intravenous injections every 6 hours. Continuous intravenous infusion was more effective than continuous intramuscular drip. No patient failed to respond to ACTH by the intravenous route and none was refractory to subsequent treatment with this drug. The authors consider that ACTH is effective by the intravenous route in one-tenth to one-twentieth of dosage required for intramuscular administration. The reasons for this difference are discussed, and the authors suggest that the greater effectiveness of intravenous infusion is due to the more continuous adrenal cortical stimulation and to the fact that destruction does not occur at the injection site.

C. E. Quin.

The Effect of Cortisone on the Lesions of Periarteritis Nodosa. BAGGENSTOSS, A. H., SHICK, R. M., and POLLEY, H. F. (1951). *Amer. J. Path.*, **27**, 537. 14 figs, 25 refs.

Treatment with cortisone of two cases of polyarteritis nodosa resulted in improvement of subjective symptoms with fall in temperature and lowering of erythrocyte sedimentation rate. Improvement was prompt, but cessation of treatment was followed by partial relapse. Active lesions were demonstrated by biopsy, but at necropsy only healed lesions were found. Death was due to the ischaemic effect of numerous healed lesions. In cases previously described there were widespread healed lesions. The present cases differed from spontaneously healed cases in the rapidity of healing—3 weeks and 3 months respectively.

The treatment caused atrophy of the testes, adrenal glands, and pituitary. *D. M. Pryce.*

Joint Temperature Measurement in the Evaluation of Anti-arthritic Agents. HOLLANDER, J. L., STONER, E. K., BROWN, E. M., and DEMOOR, P. (1951). *J. clin. Invest.*, **30**, 701. 6 figs, 8 refs.

The authors consider that criteria for judging improvement during drug treatment in rheumatoid arthritis are unsatisfactory. They record studies of the internal temperature of affected joints, suggesting that such measurements may prove more valuable. Previous work had shown that the internal temperature of a rheumatoid arthritic joint varies little from day to day under standard conditions, except when changes in the activity of the

disease occur. To determine the temperature a filamentous copper-constantin thermocouple was inserted into the joint space through the bore of an aspirating needle, an electronic potentiometer automatically recording the temperature readings.

The effect of various anti-rheumatic agents was studied, usually in patients with an affected knee-joint. Throughout the observation period daily temperatures were recorded in 21 patients with active rheumatoid arthritis. Eleven of these received cortisone parenterally (300 mg. on the first day, then 100 mg. daily) and ten patients received ACTH (80 mg. daily). In addition, cortisone acetate tablets were given orally to six patients with rheumatoid arthritis (150 mg. daily for 3 days, then 100 mg. daily), and a further eight patients received various supposedly anti-arthritic steroids.

In all the patients given ACTH or cortisone parenterally a fall in joint temperature from a minimum of 0·7° C. to a maximum of 2·7° C. (mean 1·4° C.), was recorded, within 24 hours. During the pre-injection period there had been a maximum fluctuation of 0·4° C. Joint temperature continued to decrease, and approached normal levels in 3 to 5 days. The fall preceded detectable clinical improvement in fourteen of the 21 patients, and in all but two preceded by some days any significant change in erythrocyte sedimentation rate. In all cases joint temperature began to rise within 24 to 48 hours of cessation of treatment; this rise preceded clinical relapse in seventeen instances. In fourteen patients joint temperature had returned to pre-treatment levels within 1 week of stopping cortisone or ACTH therapy. In all six patients receiving cortisone orally a marked fall in joint temperature was noted within 48 hours. The steroids used were 16-dehydropregnenolone acetate, 21-acetoxypregnenolone, Δ-5-pregnenolone, and testosterone propionate, and the eight patients who received them believed they were receiving cortisone. None of these agents produced any significant fall in joint temperature, nor was there any clinical improvement. In each case a prompt and marked fall occurred after cortisone.

The authors suggest that serial joint temperature determination might provide a rapid and relatively simple test of drug effectiveness in active rheumatoid arthritis. By this criterion no other drug has been found to have an effect comparable to that of ACTH or cortisone; and it is shown that oral administration of cortisone is comparable in effectiveness with parenteral administration. *Kenneth Stone.*

Prolonged Uninterrupted Cortisone Therapy in Rheumatoid Arthritis. BOLAND, E. W. (1951). *Brit. med. J.*, 2, 191. 30 refs.

The use of cortisone in the treatment of rheumatoid arthritis is beset with problems, including the withdrawal effects and relapse when the hormone is discontinued. For sustained improvement in a chronic disease such as rheumatoid arthritis it appears that cortisone must be given more or less continuously; but uninterrupted administration over long periods is liable to produce unpleasant, and sometimes dangerous, side-effects.

The author has treated sixty patients with rheumatoid arthritis with cortisone uninterruptedly for 6 to 15 months. Large suppressive doses were used, followed gradually by reduced dosage, and finally by smaller maintenance doses. In this way adequate degrees of therapeutic control were maintained in a majority of cases. The ability to maintain satisfactory improvement varied indirectly, in general, with the severity of the rheumatoid arthritis. In 47 per cent. of severe cases very marked or marked anti-rheumatic response was maintained for long periods. This was so also in 70 per cent. of moderately severe cases and in 92 per cent. of moderate or mild cases. It was found that adverse hormonal side-effects often developed, and were the chief obstacles to better results in the more severe cases in which relatively large maintenance doses were required to support satisfactory improvement. Unwanted side-effects developed also in 40 per cent. of all cases at some time during treatment, although most of these reactions were of a comparatively mild type and disappeared or lessened when the dosage of cortisone was reduced. It was unfortunate, however, that the lower dosage often, as would be expected, resulted in a clinical deterioration in the arthritis.

During prolonged cortisone therapy, evidence of functional suppression of the adrenal cortex was present, as indicated by a decreased response of circulating eosinophils to exogenous ACTH. Such depression of function, however, was found to be of a temporary nature, and in patients from whom cortisone was withdrawn after 6 to 14 months of continuous administration cortical function tests returned to normal within periods ranging from 10 to 90 days.

The author points out that as experience with hormone therapy of this type expands, it becomes increasingly evident that there are distinct limitations, difficulties, and dangers in its long-term administration. In the present state of knowledge it appears that cortisone may be employed as a powerful weapon in the management of rheumatoid arthritis in many cases, but it should not be considered as the treatment of choice in most cases, and not as a cure in any case.

[This paper reports the largest and longest series of cases treated with cortisone to date; the author was a pioneer in its clinical development. It is therefore of great importance, and should be read by all clinical workers in this field.] *W. S. C. Copeman.*

Intra-articular Injection of Cortisone and ACTH in Inflammatory Rheumatism. (Injections intra-articulaires de cortisone et d'ACTH dans les rhumatismes inflammatoires.) FORESTIER, J., CERTONCINY, A., and JACQUELINE, F. (1951). *Rev. Rhum.*, **18**, 207.

Investigation of the effect of intra-articular cortisone was carried out in five patients. The authors had previously noted that cortisone, while exerting its effect on rheumatoid arthritis or similar conditions, caused no change in joint effusions. [This is not the experience of other workers.] They now show that the hormone is equally ineffectual in this respect when injected into the joints. Tolerance to the injection was good: there was no increase of pain or swelling, although one joint received a total dose of 225 mg. Cell counts of the effusion fluids showed no consistent changes after injection of cortisone either in total or differential values.

ACTH, in doses of 20 mg., was injected into hydrarthroses in three patients to determine the permeability of the synovial membrane to this substance. A drop in the eosinophil count, comparable with that occurring after subcutaneous injection of the same

quantity into the same subjects, was observed. The ACTH molecule is large, and it is surprising to find that it so readily diffuses through synovial membrane: the explanation may be that the active part is a much smaller molecule.

Insulin was given by the intra-articular route in two patients. Blood sugar estimations showed a lowering of values after the injection, and a rise to the original level or above in 2 to 4 hours. In one case, a subcutaneous injection of the same dose (10 units) produced a comparable fall. In both cases there was a drop in the eosinophil count after injections. *C. E. Quin.*

Effect of Large Doses of Progesterone in Rheumatoid Arthritis. VIGNOS, P. J., and DORFMAN, R. I. (1951). *Amer. J. med. Sci.*, **222**, 29. 21 refs.

During pregnancy, production of progesterone, as measured by the urinary excretion of pregnanediol, is substantially increased, and in jaundice there is impaired inactivation of progesterone with retention of progesterone metabolites. Pregnancy and jaundice may both benefit rheumatoid arthritis, and this provides the rationale for the use of progesterone in this disease.

Progesterone was given in doses of 200 to 500 mg. daily for periods of 13 to 30 days to eight women with rheumatoid arthritis. In only one case was there substantial improvement, and this was subjective only. Erythrocyte sedimentation rates and the results of other laboratory investigations were unchanged except that the one subject showing marked improvement had a moderate rise in 17-ketosteroid excretion. There were no toxic manifestations from treatment but menstruation was suppressed in all cases. The proportion of progesterone excreted as pregnanediol (measured in five subjects), was 9 to 22 per cent.

The authors conclude that progesterone in large doses produces no consistent benefit in rheumatoid arthritis and that the steroid is not solely responsible for the beneficial effects of pregnancy. [Because of differences in the methods of estimating pregnanediol and in the dosages used, the figures for urinary excretion of pregnanediol cannot be compared with the findings of Somerville and others (*Lancet*, 1950, **1**, 116) that in rheumatoid arthritis there is an abnormally high urinary excretion of parenterally administered progesterone.] *Ellis Dresner.*

Relation of Salicylate Action to Pituitary Gland Observations in Rats. VAN CAUWENBERGE, H. (1951). *Lancet*, **2**, 374. 3 figs, 8 refs.

Earlier clinical observations of the effect of intensive salicylate therapy on the urinary excretion of adrenocortical steroids, and also various independent observations of similar effects in intact rats, led the author to investigate the action of salicylates on hypophysectomized rats, in an attempt to determine the site of action of the drug. Of the 25 male hypophysectomized rats used, four were injected subcutaneously with ACTH to test the response of the adrenal glands, twelve received an injection of sodium salicylate (500 mg. per kg. body weight), and the remaining nine served as controls. The plasma-salicylate level, as estimated by Van Cauwenberge's method, rose to about 51 mg. per 100 ml. (that is, above therapeutic levels in the treatment of rheumatic fever), but no significant decrease was observed in adrenal ascorbic acid, adrenal cholesterol or in circulating eosinophils, indicating that salicylic acid had no effect on the adrenal cortex in absence of the pituitary. The expected cortical response was obtained, however, in those hypophysectomized rats injected with ACTH. The inefficacy of salicylate therapy in patients whose blood-salicylate level is high may be explained by an alteration in the hypothalamus-pituitary-adrenal system, which can be investigated not only by Thorn's test but also by a sodium-salicylate test described by Roskam and others (*Lancet*, 1951, **2**, 375). *Nancy Gough.*

A Case of Sjögren's Syndrome treated with Adrenocorticotrophic Hormone. FRENKEL, M., HELLINGA, G., and GROEN, J. (1951). *Acta endocrinol., Kbh.*, **6**, 161. 21 figs, 14 refs.

Some Histological Aspects of Formalin "Arthritis" in Rats. BOURNE, G. H. (1951). *Brit. J. exp. Biol.*, **32**, 377. 10 figs, 3 refs.

The Treatment of Rheumatoid Arthritis, Bronchial Asthma, and Various Inflammatory Disorders of the Eye with Mustine (Nitrogen Mustard). (Il trattamento dell'artrite cronica primaria dell'asma bronchiale e di alcuni processi inflammatori oculari con l'azoiprite.) CORELLI, F., and MARINOSCI, A. (1951). *Minerva med., Torino*, **42**, 430. 12 refs.

The Effect of Acute Stress on "Formalin Arthritis" in the Adrenalectomized Rat treated with Cortisone and/or Deoxycortone. (Effetti di stress acuti sulla cosi detta "artrite da formalina" nei ratti surrenectomizzati e trattati con cortisone e/o desossicorticosterone.) PATRONO, V., and MAGLIOCCA, R. (1951). *Rif. med.*, **65**, 917. 6 figs, 15 refs.

Use of Cortisone in Rheumatic Diseases. WARD, L. E. (1951). *J. Iowa med. Soc.*, **41**, 447.

Observations on the Effects of Some Steroid Compounds other than Cortisone in the Treatment of Patients with Rheumatoid Arthritis. LEFKOVITS, A. M., and BELLOTT, A. L. (1951). *Memphis med. J.*, **26**, 161. 2 figs, 7 refs.

Clinical Effects of Δ-5-Pregnenolone in Rheumatoid Arthritis. HIGGINS, A. R., JONES, R. E., and SMITH, T. W. D. (1951). *U.S. armed Forces med. J.*, **11**, 1717.

ACTH and Cortisone in the Treatment of the Shoulder-Hand Syndrome. SIGLER, J. W., and ENSIGN, D. C. (1951). *J. Mich. med. Soc.*, **50**, 1038. 6 figs, 7 refs.

Experimental Arthritis: A Method of Measuring Limb Volume in Rats. [In English.] BERGEL, F., PARKES, M. W., and WRIGLEY, F. (1951). *Arch. int. Pharmacodyn.*, **87**, 339. 3 figs, 3 refs.

Felty's Syndrome Treated with ACTH. [In English.] BICHELL, J., and KISSMEYER-NIELSEN, F. (1951). *Acta haemat., Basel*, **6**, 65. 1 fig., 21 refs.

ACTH and Cortisone in Rheumatoid Arthritis. Effects on Blood Protein Pattern, Serological Reactions, and Bone Marrow Reticulum. [In English.] BERGLUND, K., NORDENSON, N. G., and OLHAGEN, B. (1951). *Acta endocrinol., Kbh.*, **8**, 1. 3 figs, 48 refs.

The Probability that Compound F (17-Hydroxycorticosterone) is the Hormone produced by the Normal Human Adrenal Cortex. CONN, J. W., LOUIS, L. H., and FAJANS, S. S. (1951). *Science*, **113**, 713. 1 fig, 8 refs.

The metabolic effects of giving Compound F, 400 mg. daily by mouth for 4 days, to a healthy volunteer have been studied. Excretion of sodium and of chloride was reduced and oedema developed. Excretion of nitrogen, sulphur, glucose, and uric acid were increased, and output of 17-ketosteroids and of 11-oxysteroids was doubled. Eosinophil cells were absent from the blood. The effects of ACTH administration were closely simulated. The only important difference between the actions of ACTH and of Compound F was in the esterified serum cholesterol levels which was reduced by the former but was not affected by the latter. This difference is understandable if the esterified cholesterol of serum is a precursor of adrenal hormone.

Free Compound F is as active intramuscularly as by mouth, but the acetate is relatively inactive when given intramuscularly, though active by mouth.

The authors consider that these findings are a strong indication that Compound F is the substance normally secreted by the adrenal cortex when ACTH is administered. *C. L. Cope.*

Effect of Salicylates on the Pituitary and Suprarenal Glands. HETZEL, B. S., and HINE, D. C. (1951). *Lancet*, **2**, 94. 1 fig., 29 refs.

This investigation was undertaken at the Institute of Medical and Veterinary Science, Adelaide, following a recent report of the development of Cushing's syndrome in a patient treated with aspirin (5 g. per day) for rheumatic fever. Experiments have been made to determine whether salicylates in the therapeutic dosage have an effect on the pituitary and adrenal glands (shown by removal of ascorbic acid from the adrenals) and whether this effect could be abolished by hypophysectomy or by preliminary treatment with adrenal cortical hormone (which is known to prevent the normal depletion of ascorbic acid by activity of the pituitary and adrenal glands). Wistar rats were used and the methods employed were all standard surgical and biochemical techniques. Sodium salicylate and sodium *p*-aminosalicylate were administered in amounts adequate to maintain a blood salicylate level of 30 to 40 mg. per 100 ml., which is within the range attained in patients under treatment for rheumatic fever.

Salicylate caused significant depletion of adrenal ascorbic acid even more marked than that due to insulin, which is a known stimulant of the pituitary and adrenal glands; the effects was directly proportional to the dosage. Other sodium salts had a slight action, but not comparable with that of sodium salicylate; calcium acetylsalicylate and sodium *p*-aminosalicylate were highly active.

Statistical analysis showed no significant difference between the adrenal ascorbic acid of normal rats and that of hypophysectomized rats treated with sodium salicylate, indicating that the mediation of the pituitary is essential. Preliminary treatment with cortisone tended to inhibit the effect of salicylates.

These results suggest that the beneficial results of salicylate therapy are due to activation of the pituitary and adrenal glands, leading to the production of cortisone-like steroids. *Nancy Gough.*

Cortisone and ACTH in Essential Hypertension. Establishment of Renal Glycosuria. DUSTAN, H., CORCORAN, A. C., TAYLOR, R. D., and PAGE, I. H. (1951). *Arch. intern. Med.*, **87**, 627. 1 fig., 14 refs.

Of four patients with severe essential hypertension, two were given cortisone and two ACTH; in each case the dose was 100 mg. per day. The effect of this treatment on blood pressure, renal function, and some serum levels was studied. The cases were selected because of their known stability of function and blood-pressure level; dietary intake was kept constant and treatment was not started until after an adequate control period. Blood-pressure readings showed no dramatic change. There was a reduction in systolic pressure in one patient receiving cortisone, but this effect could not be repeated by a subsequent course of treatment. The other patients showed no significant change either during or after treatment. An attempt has been made at statistical analysis of the results.

No definite effect on the concentrating power of the kidneys or on the degree of proteinuria was observed during or after treatment; nor were any consistent changes of significance observed in the estimations of renal blood flow, filtration traction, or tubular secretory capacity for *para*-aminohippurate. The tubular secretory capacity for glucose, however, was altered, being increased in one patient having cortisone and somewhat diminished in the other three; it persisted at a low level in them afterwards. Glycosuria appeared in these three patients during treatment and persisted after treatment was stopped; although the blood glucose levels, fasting and 2½ hours after meals, rose during treatment, they did not become abnormally high, and the glycosuria appeared to be due to depression of tubular reabsorption of glucose.

The patients receiving ACTH showed an increase in the excretion of urinary corticoids; no definite change occurred in those receiving cortisone. In all four patients the serum cholesterol level diminished during treatment and rose above the original level after treatment. No other significant changes in serum level were observed. *B. E. W. Mace.*

Absorption of Hormone Implants in Man. BISHOP, P. M. F., and FOLLEY, S. J. (1951). *Lancet*, **2**, 229. 8 figs, 20 refs.

The rate of absorption of hormone pellets implanted subcutaneously has been determined. Pellets were weighed before sterilization and again when removed at varying times after implantation. Correction was made for the " ghost " produced by some types of pellet.

Fused testosterone 100-mg. pellets are absorbed at about 1·1 mg. daily. Compressed tablets are absorbed at the same rate at first, but more irregularly later. Absorption of testosterone propionate 100-mg. pellets, either fused or compressed, is about 0·6 mg. daily for the first 80 days.

Absorption of oestradiol was more irregular and slower, averaging about 0·24 per cent. per day. At 240 days only about 50 per cent. was absorbed. The rate for the propionate was similar. Absorption from a 100-mg. pellet of stilboestrol or of hexoestrol is about 1 mg. daily. Progesterone is too frequently extruded for

satisfactory observations to be made. Fused deoxycortone tablets of 100 mg. absorb at the rate of about 0·4 mg. daily, less than 50 per cent. being absorbed in 220 days. Rate of absorption appears to be well related to the surface area of the pellets remaining at the time.

C. L. Cope.

An Extra-adrenal Action of Adrenotropic Hormone. SELYE, H. (1951). *Nature, Lond.*, **168**, 149. 6 refs.

Previous experiments by the author have shown that stress causes involution of the thymus during the first stage of the " alarm " reaction. This can be prevented by adrenalectomy, but it occurs in the absence of the adrenal glands if adrenocortical extract is given. In the present experiment 120 female rats were divided into four groups and adrenalectomy was performed upon all of them. One group received hypertensinogen, which was used as representative of a non-hormonal protein; of the other three groups, one received ACTH alone, one ACTH together with cortisone, and the other was given hypertensinogen with cortisone. In none of the groups did a significant loss of body weight occur. Neither ACTH nor hypertensinogen produced any significant involution of the thymus, and cortisone when given in conjunction with hypertensinogen caused only a mild degree of thymolysis; but cortisone and ACTH together caused a significant increase in involution, which was measured by weighing, and confirmed by histological examination.

H. Herxheimer.

Effect of ACTH and Cortisone on Certain Immunologic Mechanisms including Reversed Anaphylaxis. ARBESMAN, C. E., NETER, E., and BERTRAM, L. F. (1951). *J. Allergy*, **22**, 340. 13 refs.

Forssman antibodies were prepared and the minimal amount necessary to produce fatal shock by intracardial injection determined in normal guinea-pigs. This amount varied from 0·25 to 1 ml. Later, ACTH was injected in doses of 0·1 to 20 mg. 8 to 24 hours before the intracardial injection of Forssman antibodies. Doses between 0·5 and 2 mg. seemed to give some protection, but this effect was absent with higher and lower doses. Cortisone had no effect. In another series of experiments reversed anaphylaxis was produced by the injection of rabbit antiserum into guinea-pigs. Here thirteen of the twenty untreated animals died in shock, whereas of the twenty treated with 6 and 10 mg. ACTH, only six died. Under cortisone one animal out of twenty died, compared with eight when untreated. In ordinary active and passive anaphylaxis no protective effect of ACTH or cortisone was found. These substances were also given early during the period of sensitization, and the absence of any effect shows that they do not prevent the formation of antibodies. In three ragweed-sensitive patients who were treated with about 100 mg. ACTH for one week the reagin titre of the serum did not change.

H. Herxheimer.

Lethal Infection with Coxsackie Virus of Adult Mice given Cortisone. KILBOURNE, E. D., and HORSFALL, F. L. (1951). *Proc. Soc. exp. Biol., N.Y.*, **77**, 135. 3 refs.

The fact that the adult mouse has proved to be insusceptible to Coxsackie virus infection led the authors to investigate whether previous injection of cortisone would affect this insusceptibility. Experiments were carried out on Rockefeller Institute Swiss mice—both " suckling " mice (less than 1 day old) and " adult " mice which were sexually mature, of an average weight of 6 g., and 3 to 4 weeks old. Two strains of Coxsackie virus—Conn. No. 5 and RB—were used. Antisera for the neutralization test were heated at 56° C. for 30 minutes. Cortisone acetate was injected subcutaneously in 2·5 to 5 mg. doses; most of the adult mice survived this dose for at least 8 days, when the experiment was terminated. Pfanstiehl peptone broth and 0·85 per cent. NaCl buffered to *p*H 7·2 with phosphate were used for control injections.

One subcutaneous injection of cortisone was given to mice 1 to 2 hours before inoculation of the virus. Light ether anaesthesia was induced when mice were injected by the intracerebral route. Control groups of mice were given injections of both cortisone and broth in quantities and by routes identical with those employed in virus-inoculated animals. When the intraperitoneal route was used the viral suspensions were administered in amounts approximately proportional to the size of the mice inoculated (0·05 ml. virus suspension to 1·5 g. body weight). All viral inocula contained penicillin and streptomycin and were bacteriologically sterile.

Three days after inoculation all mice given cortisone and virus were dead, while controls given either virus or cortisone were alive after 8 days. It has been ascertained that in cortisone-injected mice viral multiplication took place, the lethal effect was serially transmissible, and multiplication of virus and lethal effect could be neutralized by specific antiserum. It was found also that 17-week-old mice weighing 35 g. are sensitive to the lethal infection if they have previously been given an injection of 7·5 mg. cortisone. The infection of the adult mice pretreated with cortisone took place also with Coxsackie virus which had not previously been passed through infant mice, but which was derived directly from a human source (stool).

Intraperitoneal injection proved fatal in 3 days, while mice receiving virus by the intracerebral route succumbed more slowly, dying 7 days after inoculation. It should be pointed out, however, that the intracerebral inoculation was only one-tenth the volume of that given intraperitoneally. A 1 in 100 dilution of brain tissue from mice which had received an intraperitoneal injection of infected stool promptly killed all animals when passed with normal mouse serum, but caused no evident disease or death in the presence of specific immune serum against the RB strain of virus.

Negative results were obtained from control mice in all experiments.

Observations on the adult mice pretreated with cortisone and infected with Coxsackie virus revealed that 2 to 3 days following inoculation some animals became temporarily hyperexcitable and showed huddling ruffled fur, arched backs, and laboured respiration with progressive unresponsiveness and lethargy proceeding to stupor and sudden death. Paralysis, tremor, and convulsions were not, however, noticed.

J. W. Czekalowski.

Cortical Secretion of the Isolated Perfused Adrenal. VOGT, M. (1951). *J. Physiol., Lond.*, **113**, 129. 12 figs, 38 refs.

The main object of this investigation was to determine whether substances other than adrenocorticotrophic hormone (ACTH) can exert a humoral control on the

adrenal cortex, a tissue which lacks secretory nerves. The investigation was carried out by subjecting the isolated perfused adrenal gland of the dog to the action of substances of physiological interest. Perfusion was completed with a Dale-Schuster pump filled with blood from the same animal. Drugs were either added to the reservoir of the perfusion system or infused straight into the arterial cannula. The adrenal effluent was centrifuged and the plasma assayed for cortical hormone on adrenalectomized rats, the mean survival time at low temperature being used as measure of potency. The concentration of adrenaline in plasma prepared from adrenal effluent was assayed on the rabbit intestine.

Before the administration of the series of drugs, it was shown that the perfused adrenal secretes cortical hormone at a fairly high and steady speed without being supplied with ACTH. The "standard" material for comparison was whole-gland extract, since neither Compound E (Kendall) nor deoxycortone esters have the same effect as whole-gland extract on the survival of adrenalectomized rats kept at low temperature. The slopes of the dose-response curves with the synthetic materials were not the same as that with whole gland extract. When the adrenal cortex of the dog is supplied with ACTH (24 to 54 mg. per 100 ml. blood), there is an immediate increase in hormone production. After withdrawal of ACTH there is little reduction in its secretion for at least 2 hours. A rise in the blood sugar or lactate level did not produce any direct effect on the rate of cortical secretion. Of the other organic substances tested at naturally occurring dose levels, amino-acids, sodium ascorbate, and adrenaline were without effect on the output of hormone in the perfused gland. Adenosine triphosphate and creatine phosphate, however, stimulated the activity of the cortex for a period outlasting the intra-arterial infusion of the compound by about 15 minutes. These compounds are substances with readily available energy and compare with adenosine, adenosine diphosphate and inorganic phosphate, all of which were without effect.

Of the naturally occurring constituents of plasma tested, only inorganic kations proved to be endowed with a direct action on the adrenal cortex. The rate of production of cortical hormone was accelerated by a decrease in the sodium potassium ratio from its normal figure of approximately 45 to 10 or less. This effect is obtained by increasing the potassium without altering the sodium content, but not by reducing plasma sodium even to levels below those observed in adrenalectomized dogs. Of the other compounds tested, nicotine, colchicine, and morphine failed to stimulate secretion in the perfused adrenal. Their *in vivo* action, therefore, must be due to the release of ACTH. On the other hand, histamine in large doses sometimes stimulated the adrenal cortex, but it is certain that such concentrations of plasma histamine (10 mg. acid phosphate per 100 ml. of plasma) do not normally occur, even in adrenalectomized animals. *G. B. West.*

Effect of Cortisone on Survival of Skin Homografts in Rabbits. BILLINGHAM, R. E., KROHN, P. L., and MEDAWAR, P. V. (1951). *Brit. med. J.*, **1**, 1157. 3 figs, 16 refs.

Experiments are described which demonstrate the effect of a daily dose of 10 mg. cortisone on the growth and organization of autografts and the survival time of homografts in the rabbit. Grafts were transplanted from a donor to two rabbits, all three being of wide genetic disparity; at the same time autografts were implanted alternately with these homografts. One of the recipients acted as control; the other received cortisone from the day after operation. The homografts carried by the cortisone-treated animals survived for about 25 days, while those carried by the controls were destroyed within 10 days. The control animals, being now immunized, were given cortisone and the transplanting was repeated 4 days later. These homografts survived little longer than the previous ones.

It was found that cortisone retarded the development of granulation tissue in the graft bed. The primary healing of the autografts was much weakened; there was suppression of the inflammatory processes that normally accompany healing and depression of epithelial mitotic activity. It appears that cortisone retards the rate of the processes which normally occur with healing, but does not alter their nature. The homografts in the cortisone-treated animals were found to provoke a relatively feeble and chronic reaction of uncertain progress, compared with the acute process seen in the controls. The inflammatory reaction was subdued and lymphocytic infiltration much less marked, but, again, the fundamental nature of these processes remains unchanged.

The authors suggest that these effects are partly due to the smaller blood supply and invasive activity which was noted in the autografts; other factors are the partial suppression of the immune response and the thwarting of inflammatory reactions by cortisone. On immunized animals, in the second experiments, homografts survived much less well under cortisone. Delay in the development of the immune state would, therefore, seem to be an important factor in the threefold or fourfold prolongation of the life of homografts by cortisone.

B. E. W. Mace.

Influence of Thyroxine on the Desensitising Action of ACTH and of Cortisone in B.C.G.-Infected Guinea-pigs. LONG, D. A., MILES, A. A., and PERRY, W. L. M. (1951). *Lancet*, **1**, 1392. 3 figs, 3 refs.

Albino guinea-pigs in groups of five to fifteen were given 2 mg. wet weight B.C.G. vaccine intramuscularly and were tested for sensitivity 28 days later with tuberculin by a multiple-dose method. The animals were maintained on an ascorbic-acid-free basic diet, the vitamin being supplied by unlimited cabbage. The diameter of the tuberculin lesions after 24 hours was found to be proportional to the logarithm of the dose. By plotting the mean lesion diameter against the logarithm of the dose the position of the dose-response curve may be used to estimate the degree of sensitivity developed by the guinea-pigs.

A dose of 50 mg. propylthiouracil by mouth thrice weekly for 4 weeks had no effect on sensitivity by itself, but inhibited the desensitizing action of a single dose of cortisone (2 mg.) or of ACTH (1 international unit). A 28-day course of thyroxine sufficient to produce a mild thyrotoxicosis, caused a significant increase in sensitivity. If the thyroxine was given in an amount which did not cause any signs of thyrotoxicosis, it had no effect on the hypersensitivity, but it restored the desensitizing action of cortisone and ACTH in propylthiouracil-treated guinea-pigs. It was concluded that

thyroxine was necessary for the desensitizing action of cortisone and ACTH. *Norval Taylor.*

Chorionic Gonadotrophin, ACTH, and the Adrenal-Hyaluronidase Relationship. OPSAHL, J. C., LONG, C. H. N., and FRY, E. C. (1951). *Yale J. Biol. Med.*, **23**, 399. 8 refs.

The action of chorionic gonadotrophin on hyaluronidase was tested because there is amelioration of some of the collagen diseases during pregnancy. The spreading activity of hyaluronidase injected intradermally with indian ink into mice was inhibited by chorionic gonadotrophin injections, but further investigation appeared to demonstrate that this action was not due to the gonadotrophin itself, but to contaminating adrenocorticotrophin.

First, the inhibition produced by chorionic gonadotrophin was qualitatively like that produced by adrenocorticotrophin and was similarly unaffected by gonadectomy or hypophysectomy, but was not produced after adrenalectomy. Secondly, the inhibitory activity of the gonadotrophin was unaffected by boiling, which destroys its gonadotrophic activity but which does not destroy adrenocorticotrophic activity. Thirdly, the chorionic gonadotrophin when injected into hypophysectomized rats produced a fall in eosinophil cell count and in adrenal ascorbic acid content.

Adrenocorticotrophin has been detected in placenta, and this may be the source of that contaminating the chorionic gonadotrophin. *Peter C. Williams.*

The Effect of Cortisone on Restoration of Antibodies after their Release by an Injection of Egg Albumen in the Sensitized Rabbit. (Influence de la cortisone sur la recharge en anticorps après l'injection déchainante chez le lapin sensibilisé a l'ovalbumine.) HALPERN, B. N., MAURIC, G., HOLTZER, A., and BRIOT, M. (1951). *Acta allerg., Kbh.*, **4**, 207. 2 figs, 18 refs.

The action of cortisone on antibody formation in the rabbit was investigated by studying the recovery of the antibody titre after it had been depressed by injection of an adequate dose of antigen. Two groups of rabbits, eleven and twelve in number respectively, were sensitized to crystalline egg albumen and the theoretical total amount of antigen required for saturation of the antibodies was estimated from the antigen-antibody equivalence. After the injection the antibody titre and the leucocyte count were taken at 1 hour and then every 24 hours for 6 days. Subcutaneous injections of 10 to 25 mg. cortisone per kg. were given, starting 70 minutes after the shock dose and then 12-hourly for 6 days. In the controls the antibody titre fell to nearly zero for 24 hours with complete recovery in 6 days; it was associated with a neutropenia at 1 hour succeeded by a neutrophil leucocytosis at 24 hours with a lymphocytosis, the count returning to normal in 48 hours. The results differed in the cortisone-treated animals, the antibody titre being 17·2 per cent. of the initial level at 24 hours compared with 0·9 per cent. in the controls, and at 48 hours the titre was 36·3 per cent. as compared with 9 per cent. in the controls. Thereafter, the position was reversed, the titre rising from 39 per cent. at 72 hours to 110 per cent. at 120 hours in the controls, whereas in the cortisone-treated animals it rose from 43·5 per cent. to 56·4 per cent. There was a neutropenia in the cortisone-treated animals at 1 hour succeeded by an even greater neutrophil leucocytosis at 24 hours, while the lymphocyte count fell to −76 per cent. of the initial level and remained depressed during treatment.

Two phases of antibody response under cortisone were shown, the first phase lasting 48 hours during which the recovery of the antibody titre was greater than in the controls and was associated with a lymphocytopenia, followed by a second phase when the recovery was far less than in the controls. The initial rise corresponds with the fall in lymphocyte count, and the second phase may be explained by the demonstration by others that there is an inhibition of the antibody response when cortisone is given during the sensitization period, which suggests that the effect after 3 days is due to an inhibition of the reticulo-endothelial system. *J. Pepys.*

Effects of Adrenocorticotropic Hormone and Cortisone in Patients with Tuberculosis. LEMAISTRE, C. A., TOMPSETT, R., MUSCHENHEIM, C., MOORE, J. A., and MCDERMOTT, W. (1951). *J. clin. Invest.*, **30**, 445. 9 figs, 10 refs.

Seven patients with advanced pulmonary tuberculosis were treated with ACTH or cortisone in an attempt to evaluate the participation of host mechanisms in tuberculous disease. In order that reliance should not be placed entirely upon *x*-ray changes and other clinical factors which are difficult to assess, patients with active tuberculous laryngitis were included in the study. Each patient received 100 mg. hormone intramuscularly in four equally divided doses at 6-hourly intervals for an initial 10-day period: four patients received ACTH and three cortisone.

During the period of administration of hormones, rapid amelioration and subsequent disappearance of the constitutional manifestations of acute illness were witnessed. Patients became afebrile, but similar constitutional improvement was seen in two patients who were initially afebrile. In patients with laryngitis the symptoms abated at once, and subsequently the lesions were observed to become acquiescent. Decrease in density of *x*-ray shadows was seen in five patients. Reversal of tuberculin skin sensitivity was observed in three out of the six patients tested.

On withdrawal of the hormone the signs and symptoms of acute illness rapidly returned and were as severe as or even worse than before. In the larynx, oedema and inflammation swiftly recurred on withdrawal of the hormones. The return of tuberculo-protein skin sensitivity was delayed for several weeks after cessation of hormone administration. Within 3 weeks after the completion of hormone treatment significant increases, both in concentration of serum gamma globulin and in the titre of tuberculin haemagglutinating antibodies, were noted in three of the seven patients.

Further administration of hormones demonstrated that the improved state was temporary and could not be indefinitely maintained. In two patients with laryngitis complete healing occurred after the administration of streptomycin; the bacilli in these two cases were subsequently found to be streptomycin-sensitive. [The reaction of the group of patients as a whole to previous or subsequent streptomycin therapy does not emerge very clearly from the article, but the work was intended to evaluate the effect of the hormones given alone. It is pointed out that variations in the technique of hormone

administration and the effect of their combination with other agents have yet to be evaluated.] *L. E. Houghton.*

Effect of Cortisone on Pneumococcal Bacteraemia. WHITE, R. G., and MARSHALL, A. H. E. (1951). *Lancet*, **1**, 891. 4 figs, 7 refs.

The authors report their investigation of the effect of cortisone on pneumococcal bacteraemia. Into the ear vein of each of eight rabbits 1 ml. of a broth culture of pneumococci was injected. The animals were paired, and one of each pair received cortisone while the other served as an untreated control. The treated animals were given cortisone in a dose of 15 to 20 mg. 20 hours and 1 hour before the injection of the culture, and 24 and 48 hours after the injection (if the animals were still alive). At varying intervals 1 ml. of blood was withdrawn from the vein of the opposite ear and the number of organisms in the sample estimated by the pour-plate technique.

In the control animals the number of organisms diminished rapidly; in the cortisone-treated group there was a slight initial fall, but thereafter a rapid increase, in the bacterial content of successive samples. The results of one experiment are given below.

Time after Injection	Organisms per ml. (thousands)	
	Control	Treated
Immediately	5,600·0	4,900
10 minutes	800·0	774
1 hr 20 min.	20·7	120
3 hrs	9·3	414
5 hrs	2·5	1,400
24 hrs	1·2	13,000

G. B. Forbes.

Cortisone and Pulmonary Tuberculosis. POPP, C. G., OTTOSEN, P., and BRACHER, C. A. (1951). *J. Amer. med. Ass.*, **147**, 241. 4 figs, 4 refs.

In 1947 a female aged 64 who had had rheumatoid arthritis since 1935 was admitted to a sanatorium with active pulmonary tuberculosis. Tubercle bacilli were never found in the sputum, and she was discharged from the institution in 1948.

In 1950 she was readmitted: no change was noted in the radiological appearances and the results of further sputum examinations were negative. Because her joints were very painful, cortisone was given in the usual dosage. Her arthritis, and a secondary anaemia, improved considerably, but relapse occurred 3 weeks after treatment was stopped and a second course was started. After about 1,500 mg. had been given the patient had a haemoptysis. Radiological examination showed that there was now cavitation in the left apex, and for the first time the sputum contained tubercle bacilli. Streptomycin and *p*-aminosalicylic acid were given, and 3 months later a radiograph showed that the cavity had almost completely healed.

In this case it appears that the administration of cortisone resulted in the reactivation of a previously well-healed tuberculous lesion. *B. E. W. Mace.*

Cortisone in the Treatment of Toxaemia of Pregnancy. A Study of Eight Cases. MOORE, H., JESSOP, W. J. E., O'DONOVAN, D. K., BARRY, A. P., QUINN, B., and DRURY, M. I. (1951). *Brit. med. J.*, **1**, 841. 8 figs, 16 refs.

The authors state that toxaemia of pregnancy may perhaps in part be explained on the hypothesis that it is a manifestation of Selye's general adaptation syndrome, the stress being some unknown (possibly biochemical) factor related to pregnancy. Further, the somewhat conflicting evidence on the role of the adrenals in this condition might be held to justify a trial of cortisone. Fauvet noted that the adrenal glands were below normal size in fatal cases of eclampsia, and Fauvet and Munzer reported a low blood concentration of adrenocorticotrophic hormone in eclampsia. On the other hand Venning has brought forward evidence that the adrenals are hyperactive in normal later pregnancy, and Tobian has observed a high urinary level of mineral-controlling corticoids in pregnant women with oedema due to toxaemia. There is, too, a clinical resemblance between toxaemia of pregnancy and intoxication with deoxycortone (DCA), in both of which there may be oedema, hypertension, and albuminuria with a normal blood urea level. Also both conditions are improved by a low sodium intake and in both there may be exacerbations if sodium intake is excessive. If pregnancy toxaemia is, at least in part, due to excessive secretion of corticoids controlling mineral metabolism, it is possible that a relative deficiency of the gluco-corticoids may be a contributing factor.

It seemed unlikely to the authors that the administration of cortisone (in some respects a salt-retaining hormone) would precipitate eclamptic convulsions by causing further water and salt retention, for diuresis and diminution of albuminuria has been noted by other workers from administration of ACTH and cortisone in acute nephritis and in nephritic patients with oedema.

The present paper describes the results obtained from the use of cortisone in eight cases of severe toxaemia. The preparation used was a microcrystalline suspension of cortisone acetate, 1 ml. of which contained 25 mg. cortisone. It was given by intramuscular injection and the dose varied from 100 to 300 mg. cortisone acetate daily. Routine treatment with rest, sedatives, magnesium sulphate, etc., was given in addition. The authors claim that the need for sedatives was immediately reduced and that the period of gestation was prolonged by from 1 to 4 weeks, this enabling a viable infant to be born. They stress, however, that the "striking improvement" after cortisone was in the clinical condition of the patient. Headache was relieved, vision when affected was improved, restlessness was controlled, and both the patient and her friends were quite certain that she was much better. On the other hand the effect on blood pressure was disappointing. In two cases in which the oedema had been reduced its place was taken by ascites; in two others the oedema which had been diminished by cortisone later increased at the same time as the ascites became apparent. Altogether ascites developed in five cases. Seven of the patients were delivered of live babies, but two of these were premature and died. All but two of the patients survived.

[The abstracter has read all the eight case reports carefully and has failed to find convincing evidence that

the administration of cortisone resulted in any benefit whatever. As to the authors' claim that it enabled pregnancy to be carried on for some weeks longer than would otherwise have been possible, the question arises whether this continuation was not sometimes, at least, at the expense of the well-being and even safety of the patient, and only to enable the cortisone trial to be extended. An example of this is in a case where there was retinal haemorrhage on admission, yet cortisone was continued for 8 days—that is, until the patient went into labour by spontaneous rupture of the membranes. She died 1 week later.] *F. J. Browne.*

Clinical Features and Response to Cortisone of Menopausal Muscular Dystrophy. SHY, G. M., and MCEACHERN, D. (1951). *J. Neurol. Neurosurg. Psychiat.*, **14**, 101. 5 figs, 9 refs.

The clinical features of a neuromuscular disorder which the authors call " menopausal muscular dystrophy" are described. They have studied twelve patients, of whom eleven were women, during the climacteric period or after. There is progressive weakness of muscles of the hip and shoulder girdles with little visible wasting, but a " soft " consistency of the affected muscles on palpation. There may be impairment of tendon reflexes associated with involved muscles: there has been no weakness of facial or bulbar muscles and no sign of involvement of the central nervous system. Creatinuria is surprisingly small. Biopsy examination of affected muscles shows a histological picture similar to that in α-tocopherol-deficient animals, with degeneration of muscle fibres which are undergoing necrotic changes.

In some of these patients there was a good therapeutic response to wheat-germ oil orally, while five received cortisone with marked improvement in muscular power. When administration of cortisone was stopped the patients relapsed within a few days; these patients were accordingly given a maintenance dose of 100 to 150 mg. of cortisone every 2 days and apparently have remained well for a period of 6 months. *J. W. Aldren Turner.*

Further Studies of the Effects of Cortisone and ACTH on Neurological Disorders. SHY, G. M., and MCEACHERN, D. (1951). *Brain*, **74**, 354. 5 refs.

Forty-five patients with various neurological disorders have been treated with cortisone or with ACTH. In three cases of myotonia dystrophica, the myotonia was abolished during treatment with cortisone, but it returned when treatment was discontinued. No improvement was noted in the dystrophic process. In a case of myotonia congenita, the severe, generalized myotonia was abolished during treatment with ACTH; it returned, however, during treatment with DCA, and decreased again under treatment with cortisone. Three cases of myasthenia gravis received cortisone. In two instances the myasthenia became much worse during treatment. Symptoms returned to their previous level when the hormone was stopped, but there was no rebound improvement. These observations may be of importance from the viewpoint of mechanism of the disease. Three patients with dermatomyositis were improved by cortisone. The degree of improvement depends, however, upon the amount of fixed tissue damage. We now look upon these cases as medical emergencies.

A profound state of muscle dystrophy may occur during the course of acute disseminated lupus erythematosus. In one case this responded remarkably to cortisone. In another case the muscle weakness was unaffected by either ACTH or cortisone, although the constitutional symptoms, such as fever, were abolished. Three cases of amyotrophic lateral sclerosis and three cases of peripheral motor neuropathy were uninfluenced by cortisone. Two cases of Raynaud's disease were treated; in one patient with induration and ulcer formation on her finger tips these skin changes cleared up, but the other patient who suffered from pure vasospasm was unaffected by the treatment. Two out of three patients with polyarteritis were improved by cortisone. Relapse occurred when the drug was discontinued.

No improvement was noted either in clinical symptoms of creatinuria in three cases of progressive muscular dystrophy of the childhood type. Seven out of eight cases of menopausal muscular dystrophy have shown striking improvement with cortisone, but maintenance dosage is necessary.—[*Authors' summary.*]

Effect of Cortisone on the Nephrotic Syndrome occurring in Diabetics. HOLMES, C. B., WALSH, G. C., BAIRD, M. M., WHITELAW, D. M., SIMPSON, W. W., and MCINTOSH H. W. (1951). *Canad. med. Ass. J.*, **65**, 26. 3 figs, 8 refs.

In this paper are described studies of three diabetic patients who had developed a nephrotic syndrome, and of the effect of cortisone on glucose tolerance, oedema, and serum and urinary protein content. The cortisone was given intramuscularly, 100 mg. daily for 37 days. In two of the patients the insulin dose was adjusted to control the level of fasting blood sugar and the degree of glycosuria; in the third patient the dose of insulin was maintained at a constant level.

Apart from the expected decrease in glucose tolerance on starting cortisone therapy, the results were, in general, inconclusive. No consistent effect was observed on the level of serum proteins, cholesterol, or non-protein nitrogen, or on haemoglobin, and no change in blood pressure or in ophthalmoscopic appearances was observed. In all three cases there was an increase in the total daily urinary protein excretion. Ketonuria was only once observed, and then in slight degree.

Clinically, in only one of the three patients was there any improvement in the nephrotic state: this was only temporary and was followed by a fatal relapse. In this patient the insulin requirement was found to decrease from the third week of treatment onwards, and possible reasons for this unexpected effect are discussed.

B. E. W. Mace.

ERRATUM

In the Bibliography to the paper by M. Kelly on " Monarticular Trauma and Rheumatoid Arthritis ", *Annals of the Rheumatic Diseases* (1951), **10**, 318, for: Bates, J. (1949). *Brit. med. J.*, **1**, 710, read: (1941).